Vol. 33 No. 169 June, 1958

ARCHIVES OF DISEASE IN CHILDHOOD

EDITORS
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LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

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ABO INCOMPATIBILITY AND HAEMOLYTIC DISEASE OF THE NEWBORN

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 5, 1957)

Since the work of Boorman, Dodd and Trinick (1949), incompatibility in the ABO system has been recognized with increasing frequency as a cause of haemolytic disease. Robinson, Phillips and Prystowsky (1951), Shumway, Miller and Young (1955), Davidsohn (1956) and others have written on this condition. And yet haemolytic disease due to ABO incompatibility is much less widely known than that due to Rhesus incompatibility. The failure widely to recognize ABO disease may be due to several reasons. Chiefly it is due to the fact that it is usually not a serious condition. In its severe degree it is uncommon. In its common form it is so slight as scarcely to be recognized. So the disease is held to be rare. Belief that a disease is rare leads to a lessened vigilance in its detection, and it is remarkable how once a disease is found to be not uncommon how quickly it becomes commonplace. Then again, that elegant test, the direct antiglobulin test of Coombs, which so readily detects haemolytic disease in blood group incompatibilities other than ABO, is usually negative by the more usual techniques. By the special technique of Rosenfield (1955), however, it may be shown to be positive. With heterospecific pregnancies with A or B incompatibility, antibodies are by definition present in the blood of the mother, although where disease is present they are believed to be of a different nature from the 'natural' antibody. In Rhesus disease the presence of antibody with Rhesus incompatibility indicates disease. It is not necessarily so in ABO disease. Moreover, no immune antibody may be detectable ante-natally in ABO disease, although it may appear after delivery. Unlike Rhesus disease, ABO disease cannot be anticipated by ante-natal testing with any certainty. Finally, it may be that the term 'physiological jaundice' makes for a too easy road to diagnostic apathy, and one that is trod too often.

It is stated by Davidsohn (1956) that ABO haemolytic disease appears in 1 in 3,000 random pregnancies and by Gunson (1956) that it accounts for 15% of all cases of haemolytic disease of the newborn. Certainly it is generally believed to be less common than disease due to Rhesus incompatibility. However, Rosenfield (1955) found laboratory evidence of abnormality attributable to ABO incompatibility in 38 cord blood specimens of 1,480 random samples.

The present small survey purports to show that clinically recognizable ABO haemolytic disease is a common condition and that it may quite often need close watching and active treatment.

Survey and Findings

This survey, conducted in a hospital which serves a population of about 60,000 of mixed European descent, deals with the period August 1, 1956, to July 19, 1957. During this time there were 1,000 live births. It is the universal practice in this locality for deliveries to be in hospital. The survey therefore covers 1,000 random live births.

During the period under review all babies judged to show the slightest jaundice within the first 24 hours after birth were reported. It was found that minimal jaundice was difficult to detect in artificial light, and it is more than likely that some escaped investigation if they became jaundiced but slightly at night toward the end of the 24-hour limit set by the terms of the survey. Nevertheless, in 1,000 live births, 21 babies were found to be recognizably jaundiced within 24 hours. Six were found to have haemolytic disease due to antibody anti-D and one to be due to anti-E, and these are excluded from the series. Fourteen babies with jaundice believed not due to Rhesus disease were investigated. It should be emphasized that no baby who became jaundiced within 24 hours is excluded from the investigation apart from the seven in whom D or E incompatibility was found. Nothing was known about the blood groups of mother or baby until early jaundice had prompted investigation.

Table 1 relates to the parity of the mother, the birth weight in pounds and ounces and the time of onset of the jaundice in hours after birth. It will be noted that in three instances first babies were involved and that one came within the World Health Organization definition of prematurity. Cases 2 and 3 were dizygotic twins of the same blood group, A. There was no difference in sex incidence. The time of onset of the jaundice varied between four and 23 hours with a mean of 14 hours. The smaller babies did not become jaundiced earlier than those of larger size.

Table 2 refers to the initial bilirubin estimation and to the maximal bilirubin estimation. Bilirubin estimations were not done at night if the jaundice did not seem to be deepening rapidly, nor were they repeated if the initial level was low and the baby not becoming more icteric.

It will be seen that we were able just to detect jaundice at a level of 4 mg. % but it was our experience that it did not become easily visible until a level of about 6 mg. % was reached. In three cases the maximal bilirubin reached the figure of 20 mg. % or over, and in these babies exchange transfusions were done. In one case, Case 6, three exchanges were required to keep the bilirubin at a safe level. The average time for the onset of jaundice in these three cases was 14 hours, which does not differ from the series as a whole.

Table 3 shows the first haemoglobin level determined after the jaundice was first reported. In no case was the haemoglobin below 15 g. %, and in the majority it was considerably higher. The most severely jaundiced did not have lower haemoglobin levels than the remainder. In twelve instances it is recorded that splenic enlargement was specifically sought. In two only was it found.

Table 4 shows the presence or absence of spherocytes in a stained smear and the osmotic fragility of the red cells in venous blood expressed as the percentage concentration of sodium chloride in which haemolysis is first apparent.

In eight instances spherocytosis is recorded as being present. It is remembered that it was also present in two further cases, Cases 2 and 3, but there is no written record of this. All cases showing spherocytosis showed haemolysis in concentration of 0·60% saline, or greater, but those showing the most obvious spherocytosis were not those with the greatest fragility. Reticulocyte counts were done in only nine of the 14 babies. In only three was the count above the normal of 4·35% (Washburn, 1941) for this age group.

Table 5 shows the reaction on a slide of the whole blood of the baby when mixed with complement inactivated normal AB serum compared with the same serum with the addition of bovine albumin (Witebsky, 1954). Thirteen of the 14 babies had blood which agglutinated with normal AB serum within 90 seconds. One baby showed no reaction where reaction might have been expected. In five there was agglutination also in the AB serum with bovine albumin.

Experience with this test has shown that it is most difficult to interpret with confidence. The agglutination may be very fine and scarcely visible. It is easily confused with rouleaux formation. The time limit of 90 seconds must be strictly enforced or false positive results will be found. Incorrect readings in our hands have been too frequent to make the test really valuable.

The direct antiglobulin test of Coombs was performed in the 14 babies in the series. In only one, Case 4, was macroscopic agglutination seen with a test carried out as described by Zuelzer and Cohen (1957).

Table 6 shows the blood groups of the babies compared with those of their mothers. It will be seen that in every one of the 14 cases of babies becoming jaundiced within the first 24 hours an incompatibility, O-A or O-B, was found. In 12 A was the incompatible, in two it was B. No attempt at subgrouping into A_1 or A_2 was made.

Table 7 shows the ABO phenotype distribution in 50 mother-child pairs randomly selected in our area. For clarity, those where incompatibility of A or B exists are marked with an asterisk. It is seen that such incompatibility was present in 10 births out of 50. If this finding is compared with Table 6 a marked and highly significant difference is obvious. That every mother in the series was group O and every baby either group A or B can scarcely be due to chance.

It might be argued that 50 random mother-child combinations is too small a number to rule out a peculiar bias in blood group distribution, but the percentage of compatible and incompatible pairs in that small number is almost identical with the number which would be expected on the basis of the ABO gene frequencies. This calculation was made and resulted in the expectation of 81% compatible mother-child pairs, assuming that mating is random and unrelated to blood groups.

Table 8 shows the maximal bilirubin level in relation to the D factor of Rhesus of the babies and their mothers. It is seen that of 14 babies jaundiced in the first 24 hours no less than seven were d/d: in common parlance, they were Rhesus negative. Using tables (Mainland, 1948) giving the confidence limit for small samples, it can be shown that this

TABLE 1

MATERNAL PARITY, BIRTH WEIGHT AND TIME OF ONSET OF JAUNDICE

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Parity of mother ..	1	2	2	1	2	2	3	3	1	2	2	4	9	2
Birth weight (lb. oz.)..	7·2	6·8	4·15	8·10	6·6	6·10	8·5	6·14	6·4	6·5	8·9	8·14	6·13	6·4
Onset of jaundice (hr. P.N.) ..	4	18	22	6	20	23	7	11	12	8	18	10	9	20

TABLE 2

INITIAL AND MAXIMAL BILIRUBIN ESTIMATIONS

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Initial bilirubin (mg.%)	6·5	8·0	5·0	8·6	11·9	13	7·0	7·5	9·2	7·0	11·3	6·4	4·0	8·6
Maximal bilirubin (mg. %)	6·5	9·0	5·0	8·6	14·6	25·0*	7·0	22·0*	10·3	20·0*	14·0	6·4	16·2	8·6

* Exchange transfusion.

TABLE 3

INITIAL HAEMOGLOBIN LEVELS

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Haemoglobin (g. %) ..	19·5	18·0	18·5	20·0	17·0	20·0*	18·5	17·0*	16·0	16·5*	16·5	19·5	15·0	19·0

* Exchange transfusion.

TABLE 4

SPHEROCYTOSIS AND OSMOTIC FRAGILITY IN BABIES

Case No.	1	2	3	4	5	6*	7	8*	9	10*	11	12	13	14
Spherocytosis ..	—	?	?	++	+	+	+	—	+	—	—	+++	+	+
Osmotic fragility (% sodium chloride)	0·64	0·64	0·60	0·60	0·80	—	0·80	0·52	0·84	0·56	0·56	0·60	0·60	—

* Exchange transfusion.

TABLE 5

WITEBSKY TEST REACTIONS

Case No.	1	2	3	4	5	6*	7	8*	9	10*	11	12	13	14
Reaction in AB serum	+	+++	+	+	+++	+	+	+	0	+++	+	+	+++	+
Reaction in AB serum + albumin ..	0	+	0	+	0	+	+	0	0	0	+	0	0	0

* Exchange transfusion.

TABLE 6

BLOOD GROUPS OF MOTHERS AND BABIES

Case No.	1	2	3	4	5	6*	7	8*	9	10*	11	12	13	14
ABO:														
Baby	A	A	A	A	B	A	A	B	A	A	A	A	A	A
Mother	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Rhesus:														
Baby	D	D	D	D	d/d	d/d	d/d	d/d	d/d	d/d	D	d/d	D	D
Mother	d/d	D	D	D	D	d/d	D	d/d	D	D	D	d/d	D	D

* Exchange transfusions.

TABLE 7
ABO PHENOTYPE DISTRIBUTION IN 50 RANDOM MOTHER-CHILD PAIRS

ABO phenotype	O-O	O-A	O-B	A-O	A-A	B-O	B-A	B-B	AB-O	AB-B	AB-A
No. of pairs	11	6*	2*	6	18	1	2*	1	1	1	1

* Incompatibility of A or B.

TABLE 8
RHESUS D FACTOR IN MOTHER AND BABIES AND MAXIMAL BILIRUBIN LEVEL

Case No.	1	2	3	4	5	6*	7	8*	9	10*	11	12	13	14
Rhesus:														
Baby	D	D	D	D	d/d	d/d	d/d	d/d	d/d	d/d	D	d/d	D	D
Mother	d/d	D	D	D	D	d/d	D	d/d	D	D	D	d/d	D	D
Bilirubin, maximal	6·5	9	5	8·6	14·6	25	7	22	10·3	20	14	6·4	16·2	8·6

* Exchange transfusion.

TABLE 9
BLOOD GROUP OF BABY AND ANTIBODY LEVEL IN MATERNAL BLOOD

Case No.	Baby	Mother		Nature of Antibody
	ABO	Anti-A	Anti-B	
1	A	—	—	—
2	A	320	40	Both resistant to neutralization. Anti-A eluted from baby's cells.
3	A	320	40	Both resistant to neutralization. Anti-A eluted from baby's cells.
4	A	40	20	Both weakly immune. Findings not too conclusive.
5	B	40	320	Anti-B is strongly immune. Anti-A weakly so.
6	A	—	—	—
7	A	640	80	Only anti-A is of immune variety.
8	B	640	80	Both antibodies strongly immune.
9	A	640	80	Both antibodies strongly immune.
10	A	640	160	Both antibodies of immune variety.
11	A	—	—	—
12	A	1,000	320	Both of immune variety. Blood taken 6 weeks after delivery.
13	A	160	40	Both antibodies of immune variety.
14	A	320	20	Anti-A is strongly immune. Blood taken 6 weeks after delivery.

observed distribution of Rhesus negative babies with jaundice and AB incompatibility is a departure from the expected in a population such as ours at a low level of significance (significant at 5% level, but scarcely so at 1% level). It will also be noted that the three babies requiring transfusion were Rhesus negative (d/d), and that the average maximal bilirubin value in this series was higher for the Rhesus negative (d/d) babies than for the D positive infants. The mean difference was 5·3 mg. %, the standard error of difference 3·20. In this small series the difference between the maximal bilirubin levels of the D positives and the Rhesus negatives (d/d) was not significant.

Table 9 illustrates the level of antibodies found in the blood of the mother. Except where indicated in the table blood samples were taken two to four days after delivery. The antibody titrations were most kindly carried out at the Ortho Research Foundation, Raritan, New Jersey, under the direction of Dr. Phillip Levine, whose comments are given in brief.

Antibody studies were carried out on the blood of the mothers of 11 of the 14 babies in the survey. It will be seen that a high titre of immune antibody is present against the factor carried by the baby with a frequency which seems far too high for it to be the result of mere chance or of immunization

unrelated to the pregnancy. However, in Case 4 the antibody levels were not very convincing, while in Case 8, where the baby was group B, immune anti-A was present in a titre of 1:640 and immune anti-B in a titre of 1:80 only.

Discussion

Investigations on the cases presented here are in some instances incomplete, but the following facts clearly emerge. The slightly lower birth weights of those requiring treatment was not a significant difference. There was no difference in the average time of onset of the jaundice in those in whom the jaundice later became severe. Late onset did not mean mild disorder. The Coombs test was positive in one baby, but this was one with a low level of bilirubin throughout. The initial haemoglobin level was no lower in those threatened with kernikterus than in the others, nor was splenic enlargement a feature of severe disease. Spherocytosis was present or absent in mild and in severe cases alike, as was an increased osmotic fragility of the red cells. Agglutination of the baby's cells in AB serum was found in the three severely affected babies, but it was also found in most of the others, including that with the lowest bilirubin. A reticulocyte count of 11% was found in one of those with marked icterus, but a similar count was found also in one of the mildest of the series. Immune anti-A was found in a titre of 1:640 in one of the babies with severe jaundice, but it was present in the same titre in a baby whose bilirubin never rose above 7 mg. %. Incompatibility of group B was present in a severe case, but was present also in a case of only moderate severity.

There was thus, in this series, no difference between the cases with severe jaundice and those with mild jaundice apart from the degree of jaundice itself.

The 14 cases where ABO incompatibility existed appeared to represent a uniform picture of the same disease manifesting itself in greater or less severity. There was no way of forecasting which would become an anxiety and which would cause no alarm. All need close watching.

The true incidence of ABO disorder is difficult to determine. Rosenfield (1955) found laboratory evidence in 38 specimens of 1,480 cord blood samples collected at random. It appeared that the disorder was present in the babies of 11% of mothers who lacked A or B when this was possessed by the foetus. The high degree of significance in the present small series for the frequency of incompatibility compared with that expected suggests that these cases, selected purely because they were clinically jaundiced, were indeed examples of ABO haemolytic disease. If this be accepted, we found ABO haemolytic disease to be clinically recognizable in one in every 71 births and likely to be present in 7% of mother-child pairs where A or B incompatibility exists.

An arbitrary limit of 24 hours was set for the onset of jaundice coming within this review. When one sees that of the 14 cases believed to have ABO haemolytic disease, four first showed jaundice at 20 hours or over, one immediately suspects that many cases of jaundice with onset after 24 hours may in fact be examples of haemolytic disease. This we have found to be so. It is clear, however, that the disorder does not always appear, in form detectable by known methods, every time that incompatibility exists. Why this curious selection occurs is at present unknown. It is likely that a combination of circumstances must exist before the disorder is manifest. It appears (Zuelzer and Cohen, 1957) that babies of subgroup A_2 escape altogether and that full maturity of the antigenic potential of A_1 is not developed in the newborn. It may be that in some babies the immune antibody does not cross the placental barrier or is neutralized in so doing by the A or B substances in the placental tissue. It may be that there is an antigenic fraction associated with, but not identical with the A and B antigens, which is present in some but not in others. Unger and Wiener (1954) have demonstrated a factor C in the ABO system, and to this factor they attribute ABO haemolytic disease. If the group O mother of a baby of group A had, herself, a mother who was of group A and a secretor one could see that she, while herself a foetus, could develop tolerance to the A antigen from being subjected to A in intrauterine life. Were this to happen one could imagine that such a mother would not herself have a baby with ABO haemolytic disease for, to her, the A factor would no longer be antigenic. Probably there is no single explanation of why the disorder does not always appear when conditions seem to be fulfilled for its appearance.

In this survey a discrepancy at a low level of significance is noted between the incidence of Rhesus negativity in mother-child incompatible babies affected with ABO haemolytic disease and what would be expected from the random distribution. If this difference be real it is difficult to explain. Until a larger series proves or disproves the significance of this observation it would be idle to speculate further.

Some would discount the levels of antibody titrations presented in Table 9, saying rightly that many normal people who have never received inoculation with human blood or tissue products

may have a high level of immune anti-A or anti-B. Nevertheless, taken in conjunction with other evidence, it does not seem that the titres found here can really be disregarded.

It is a matter for regret that we did not use the test for free homologous antibody using adult cells of the same group as the baby. At the time this survey started the value of this test (Zuelzer and Cohen, 1956) was not realized. We are now employing this test using the A or B cells of the baby's father for, if his baby is affected, he will himself possess cells upon which free antibody in the baby's serum will react; that reaction being detected by the indirect Coombs test.

Summary

From 1,000 unselected live births all babies showing jaundice in the first 24 hours were investigated. Twenty-one such babies were found. Seven were diagnosed as being examples of Rhesus haemolytic disease and these are excluded from this series. Fourteen were considered to have ABO haemolytic disease, and for this evidence is presented.

ABO haemolytic disease can occur in clinically recognizable degree as often as once in every 71 births and may arise in 7% of AB incompatible mother-child pairs. It is thus about three times more common than haemolytic disease due to Rhesus incompatibility.

There is always a reason for jaundice within 24 hours of birth. The diagnosis of 'physiological jaundice' should not be invoked to explain such a happening.

My thanks are profoundly due to many: to the nursery nurses for their unfailing enthusiasm and vigilance, to the doctors who permitted me to see their patients, to the laboratory technicians for their most painstaking work at all hours and to the staff of the medical records department. I am also most grateful to the Ortho Research Foundation and to Dr. Phillip Levine for the reports on the antibody titrations and to Dr. Carol Buck of the University of Western Ontario for the statistical examinations.

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THE DISAPPEARANCE OF FOETAL HAEMOGLOBIN IN CONGENITAL CYANOTIC HEART DISEASE

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 5, 1957)

Children with congenital cyanotic heart disease become adapted to some extent to anoxaemia. A well-recognized response is an increase of haemoglobin concentration; this increase might also be accompanied by a change in the type of haemoglobin formed. Foetal haemoglobin is more favourable than adult haemoglobin for oxygen uptake, and postnatal anoxaemia might promote the production of foetal haemoglobin in significant amounts. The observations reported here were made to test this hypothesis.

Adams (1952) found that in a group of 19 infants and children with congenital cyanotic heart disease foetal haemoglobin did not persist in greater amounts than in a group of normal children and adults. The range of age of the cyanosed group was wide and included infants, children, adolescents and an adult aged 30 years, but their control group did not include any infants, the youngest patient being 4 years old, and the oldest 70 years. Their mean values in the cyanosed and control groups (6% and 3%) exceeded the accepted upper limits of 1% to 2% in normal children and adults (Singer, Chernoff and Singer, 1951; Zannos, 1953; Huisman, Jonxis and Dozy, 1955; Jonxis and Visser, 1956).

We used the optical method of Brinkman and Jonxis (1935), with modifications (White, 1956), to estimate the proportion of foetal haemoglobin from 24 full term normal infants. We found this to be a mean value of 72% with a range of 59% to 88%; this closely agrees with figures given by Schulman, Smith and Stern (1954) and Walker and Turnbull (1955). No foetal haemoglobin was demonstrated in the blood of four normal adults.

The same method was then used to determine the proportion of foetal haemoglobin present in 25 infants and children aged from 6 weeks to 8 years with Fallot's tetralogy; the cyanosis in most of these patients was severe. During the same period 22 infants and children formed a control group.

Method

Heparinized venous blood (2·5 to 5 ml.) was collected and the cells were washed twice with 0·85% sodium chloride and then once with 1·2% sodium chloride. The cells were then mixed with distilled water, frozen overnight and subsequently allowed to thaw at room temperature. After the addition of shredded asbestos, the stroma was removed by spinning for one hour at 3,000 r.p.m.; 0·2 ml. of the supernatant fluid was then added to 4·6 ml. of ammonium hydroxide in a cuvette and, using a Gallenkamp photometer with an Ilford 608 (red) filter, an initial reading D_o was taken. Then 0·2 ml. of normal sodium hydroxide was added with rapid stirring and readings were taken over the next 10 minutes at 10-second intervals, the time interval being gradually lengthened to one minute. If foetal haemoglobin was present, readings were continued for up to three hours, the final reading being $D\alpha$. The amount of haemoglobin remaining undenatured at time (t) was calculated from the formula:

$$\text{Amount of foetal haemoglobin present} = \frac{D_t - D\alpha}{D\alpha - D_o}$$

These figures were then plotted on semi-logarithmic paper using time as the abscissa and the curve obtained was extrapolated backward to cut the ordinate at a figure representing the amount of foetal haemoglobin originally present in the sample.

Results

Foetal haemoglobin was not found in any infant or child over 7½ months old in the cyanotic or in the control groups. Variable amounts of foetal haemoglobin were found in infants under 7½ months. During this period 21 estimations were made in five cyanosed and in three control infants (Table 1).

The degree of cyanosis in the five infants was severe. All were full term infants except J.H. whose

birth weight was 3 lb. 1 oz. and gestation period 34 weeks. Foetal haemoglobin was not found in two infants (M.W. and P.C.) at 22 weeks, and in a further four infants (M.S., S.H., A.M. and R.S.) at 26 weeks; at this time only J.H. had foetal haemoglobin present (9%) and this was not detectable at 30 weeks.

TABLE 1

PERCENTAGE OF FOETAL HAEMOGLOBIN IN CYANOSED AND CONTROL INFANTS

		Age in Weeks						
		6	10	14	18	22	26	30
		%	%	%	%	%	%	%
Cyanotic Group	J.H.	61	40	24	22	21	9	0
	M.S.	—	—	—	10	—	0	—
	M.W.	44	—	—	—	0	—	—
	S.H.	—	18·5	—	—	—	0	—
	D.B.	—	—	—	7·8	—	—	—
Control Group	P.C.	64	—	—	—	0	—	—
	A.M.	54	—	—	23	—	0	—
	R.S.	—	32	—	—	—	0	—

Discussion

The oxygen curve of foetal haemoglobin lies to the left of that of adult haemoglobin, provided that the pigment is in the corpuscles (Leibson, Likhnitzky and Sax, 1936; McCarthy, 1943). This increased affinity of foetal haemoglobin for oxygen is most marked at the higher oxygen tensions. Thus, the presence of a high proportion of foetal haemoglobin is favourable for oxygen intake. Walker and Turnbull (1953, 1955) have stated that the rise in total haemoglobin which they have observed in the anoxic foetus at term was mainly due to an increased production of foetal haemoglobin. As term approached they found a rise in total haemoglobin which was proportional to a fall in oxygen saturation of the blood in the umbilical vein. Recently Rooth and Sjöstedt (1957) were unable to confirm this correlation.

Persistent postnatal anoxia usually causes a rise in total haemoglobin, thereby increasing the amount of oxygen available to the tissues; an increase in the proportion of foetal haemoglobin would augment this by further increasing the oxygen uptake in the lungs. Furthermore, at birth the mechanism for the formation of foetal haemoglobin is still active (Schulman *et al.*, 1954) and under the stimulus of persistent anoxia, foetal haemoglobin would be readily formed.

The figures for J.H. (Table 1) show that, from 14 to 27 weeks, the percentage of foetal haemoglobin remained the same while during the same period the total haemoglobin rose from 9·2 g. % to 17·5 g. %. This suggests that during this time the production of foetal haemoglobin was at least maintained.

It should be pointed out that although the method used had the disadvantage of being relatively inaccurate for amounts of foetal haemoglobin below 10% it was especially suitable for accurate measurement of larger amounts. However, foetal haemoglobin did not persist in significant amounts beyond 30 weeks in the children and infants whom we studied and the foetal pigment disappeared at about the same rate in both the cyanotic and control groups.

Summary

Blood from 25 infants and children with cyanotic congenital heart disease was tested quantitatively for foetal haemoglobin. Twenty-two normal infants and children of similar age were studied over the same period. Foetal haemoglobin was not found in any child over the age of 7½ months in either group.

We thank Dr. P. R. Evans and Dr. R. C. Mac Keith for their helpful criticisms. Some of the patients studied were under the care of Sir Russell Brock to whom we are grateful. We acknowledge with thanks advice given by Dr. J. C. White, Hammersmith Postgraduate School of Medicine, on the technique of estimation.

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BASOPHILIC LEUCOCYTES IN CHILDREN IN HEALTH AND DISEASE

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 5, 1957)

The presence of basophilic leucocytes (basophils)* in human blood was first established by Ehrlich (1891). These cells differ from other polymorphs by their slightly smaller size, by the metachromatic staining reaction of their granules, and by their slower rate of motility (Sabin, 1923). Probably less is known about the basophils than about any of the other formed elements in the blood, mainly because they are very scanty in the peripheral blood and because until 1953 there was no satisfactory method of counting them accurately. Counts based on examination of blood smears are unreliable unless very large numbers of cells are counted and consequently in most studies of the variations of leucocytes in disease the basophils have been ignored or dismissed in a few words as of no significance. In his monograph on mast cells, Michels (1938) gathered most of the information about basophils available at that time and the inaccuracy and contradictions of many of the earlier papers are readily apparent on reading this review, in which the author stigmatized much of the previous literature as 'worthless'. The few standard paediatric textbooks which do more than mention the existence of basophils merely remark on the lack of information available. For example, Nelson's *Textbook of Pediatrics* (Nelson, 1954) states that 'basophils occur in small numbers in the blood of children. Their function is unknown and they appear to have clinical significance only in that they are consistently elevated in chronic myelogenous leukemia in children'.

Recent evidence that basophils contain heparin (Behrens and Taubert, 1952; Martin and Roka, 1953) and histamine (Graham, Lowry, Wheelwright, Lenz and Parish, 1955; Code and Mitchell, 1957) throws fresh light on the function of these cells, while the introduction of a chamber-counting method by Moore and James (1953) has made it possible to measure even small changes in the numbers of circulating basophils with considerable accuracy. It therefore seemed worth while to undertake a study of these cells in the blood of children in order to determine more accurately the changes which occur in response to disease. The three diseases chosen for study were lobar pneumonia, acute rheumatism, and anaphylactoid purpura (Schönlein-Henoch syndrome), as examples of common acute diseases of varied aetiology in children.

The basophils were also counted in the blood of 67 healthy children, in order to obtain some indication of the normal variations.

Methods and Procedure

The method used was essentially that described by Moore and James (1953), except that 0·075% toluidine blue (B.D.H.) was used instead of 0·05% as recommended. The stain was adjusted to *p*H 7·75 with sodium hydroxide and filtered before the addition of saponin, which was made up as a 30% solution in 50% ethyl alcohol. Basophils, eosinophils and total leucocytes were counted simultaneously in the same counting chambers, all the counts being made by the author.

Free-flowing capillary blood obtained by finger-prick was used and all counts were made between 12 noon and 2 p.m., in nearly every case just before a meal. The only exception to this was that the initial counts in acutely ill children were made as soon as possible after admission to hospital, regardless of the time of day. Counts were made daily for the first five days after admission, at one week, and thereafter twice weekly.

The erythrocyte sedimentation rate (E.S.R.) was determined by a modification of Cutler's micro-method, except where otherwise indicated.

Healthy Children. The healthy children had been admitted to hospital for the treatment of some minor anatomical abnormality, in the great majority of

* 'Basophil' should correctly be spelled 'basiphil' since it is derived from the Greek word βάσις (basis) but the spelling 'basophil' has become established in the literature.

cases an inguinal hernia, and a smaller group who were admitted to a short-stay children's home for social reasons, usually because the mother was in hospital. There were also a few enuretic children in whom full investigation had revealed no physical cause of the symptom. None of the children had a history of allergic diseases.

Lobar Pneumonia. Cases of pneumonia had to satisfy the following criteria: (*a*) onset of symptoms within the previous four days; (*b*) leucocytosis of over 12,000 per c.mm.; (*c*) pyrexia of at least 100° F.; (*d*) radiological evidence of pulmonary consolidation.

Eleven cases of pneumonia were studied, and all were treated with penicillin injected intramuscularly; two children (Cases 4 and 5) had a sulphonamide drug in addition. Ten of the children made a rapid and uninterrupted recovery while one seriously ill child (Case 8) did not respond to penicillin but rapidly recovered when treatment was changed to oral tetracycline on the fifth day.

Acute Rheumatism. To be included, cases of acute rheumatism had to satisfy the following criteria, which also fulfil the requirements for the diagnosis of rheumatic fever laid down by Jones (1944): (*a*) duration of symptoms for one week or less; (*b*) leucocytosis; (*c*) pyrexia; (*d*) migrating polyarthritis; (*e*) presence of a significant cardiac murmur; (*f*) E.S.R. above 50 mm. in the first hour. Nine children with acute rheumatism were studied; they were treated with salicylates in a dose of approximately 1 gr. per lb. per day, and an initial course of penicillin by intramuscular injection lasting one week.

Anaphylactoid Purpura. Children with anaphylactoid purpura were included in the study if they showed the specific exanthem (Gairdner, 1948), purpura of the characteristic distribution, and one or more swollen, painful joints. No child who had had a previous attack was included. Six children satisfied the criteria (Cases 22 to 27); except where indicated the only treatment given was a course of intramuscular penicillin lasting one week. Because of the interval which usually elapsed before the child was sent into hospital it was not always possible to make the first basophil count at the beginning of the disease, but it was made within a week of onset in five children and within two weeks in the sixth (Case 27). When the first count was made, however, all the children had fresh purpura and acute joint manifestations or acute abdominal pain with tenderness and muscle guarding.

Results

Healthy Children. Counts of basophils, eosinophils and total leucocytes were made on a single occasion in each of 67 healthy children. There were 46 boys and 21 girls, their ages ranging from 6 months to 12 years. The mean basophil count for the whole group was $45{\cdot}0 \pm 2{\cdot}5$ per c.mm., with a standard deviation of $\pm 20{\cdot}1$ and a range from 13 to 94 per c.mm. The mean count for the boys was $45{\cdot}6 \pm 3{\cdot}1$ (S.D. $\pm 21{\cdot}3$) and for the girls $43{\cdot}6 \pm 3{\cdot}5$ (S.D. $\pm 17{\cdot}5$). When the children were grouped according to age, the mean counts were as follows:

Age (years)	No.	Basophils per c.mm.
-1	7	44·0
1-2	9	45·3
2-3	10	44·7
3-5	13	46·7
5-8	14	44·4
8-12	14	44·5

The basophil count thus does not alter significantly throughout childhood.

The mean eosinophil count for the whole group was $245{\cdot}8 \pm 22{\cdot}7$ per c.mm., with a standard deviation of $\pm 185{\cdot}5$, and the mean total leucocyte count was 8,390 per c.mm.

In general the eosinophil count tended to be low when the basophil count was low and high when it was high, but there were many exceptions and the numerical relationship between the two types of cell was not a close one.

Lobar Pneumonia. The results of serial basophil counts in the 11 children with lobar pneumonia are shown in Fig. 1 and Table 1. In all cases the basophil count was low on the first day, none being over 20 per c.mm. Clinical recovery was associated with a rapid rise in the basophil count to reach a maximum during the second week, when no count of less than 50 per c.mm. was recorded. Thereafter the numbers of basophils began to fall; the counts were not continued after the third week because the patients were then discharged. As can be seen from Fig. 1, the curve of the mean eosinophil counts was similar to that of the mean basophil counts, and as would be expected the total leucocyte count rapidly fell to normal. In the severely ill boy (Case 8) whose illness did not respond to penicillin, the number of basophils remained low for the first four days but increased rapidly when tetracycline was given, reaching 135 per c.mm. on the 17th day.

Acute Rheumatism. Of the nine children who fulfilled the diagnostic criteria, eight (Cases 12 to 19) pursued an uncomplicated course to recovery and

TABLE 1

SERIAL BASOPHIL COUNTS IN 11 CASES OF LOBAR PNEUMONIA

Case No.	Age (years)	Days 1	2	3	4	5	7	10	14	17	21	24
		(Basophils per c.mm.)										
1	7	16	25	37	34	38	41	66	104	78		
2	3½	13	34	38	42	44	46	78	70			
3	6½	20	28	31	31	43	75	100	63	63		
4	7	19	31	25	25	29	38	55	58	53		
5	2¼	6	13	25	47	45	72	63	61	64		
6	3	19	31	37	38	46	56	74	56			
7	2½	19	25	45	41	46	72	53	56			
8	8½	0	0	6	13	22	47	66	110	135	103	55
9	2¾	12	19	31	45	42	49	91	116	52		
10	5	12	16	31	53	52	87	91	69	66		
11	9	17	25	29	30	44	40	63	79	70		
Mean		14	22	30	36	41	57	73	77	73		

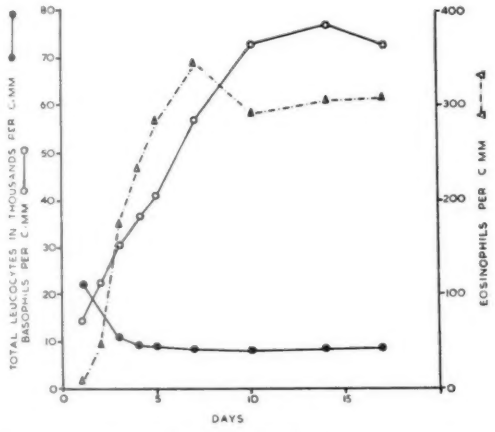

FIG. 1.—Mean basophil, eosinophil and total leucocyte counts in 11 cases of lobar pneumonia.

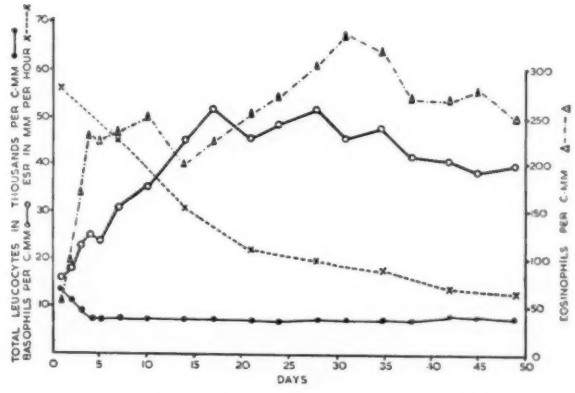

FIG. 2.—Mean basophil, eosinophil and total leucocyte counts and mean erythrocyte sedimentation rates in eight cases of acute rheumatism.

TABLE 2

SERIAL BASOPHIL COUNTS IN EIGHT CASES OF ACUTE RHEUMATISM

Case No.	Age (years)	Days 1	2	3	4	5	7	10	14	17	21	24	28	31	35	38	42	45	49
		(Basophils per c.mm.)																	
12	12	1	9	9	19	25	31	38	42	47	32	30	35	25	28	29	30	—	28
13	10	6	13	16	17	13	13	19	27	29	22	31	34	30	22	20	19	21	19
14	7½	30	22	27	28	38	37	28	28	42	49	—	59	—	63	52	48	50	56
15	11½	29	25	31	34	25	29	28	47	55	48	56	60	41	50	38	34	42	37
16	10	3	6	9	13	19	25	28	36	38	31	28	35	39	44	44	41	29	31
17	7	20	17	13	18	13	20	48	63	50	39	39	45	37	42	31	29	25	33
18	11	16	22	44	44	41	45	36	59	70	63	71	61	64	53	42	42	39	41
19	10	19	27	31	25	19	44	54	55	81	87	86	90	83	85	82	87	69	73
Mean		16	18	23	25	24	31	35	45	52	46	49	52	46	48	42	41	39	40

the changes in numbers of basophils are recorded in Fig. 2 and Table 2. As in the cases with pneumonia, the initial count in every case was low, none being above 30 per c.mm. In most cases the count remained low during the first week, rose gradually to reach a maximum in the third, fourth or fifth week, and thereafter fell slightly to a more or less stationary level. Counts were not continued beyond the seventh week of the illness as the children were usually sent home or transferred to a convalescent home on recovery.

The E.S.R. in all cases diminished steadily as recovery proceeded, being below 15 mm. per hour in six of the eight cases by the seventh week, and reaching this level soon afterwards in the other two. During the initial period of recovery (Figs 2 and 3), when the basophil count was rising to a maximum level, there was an inverse relationship between the

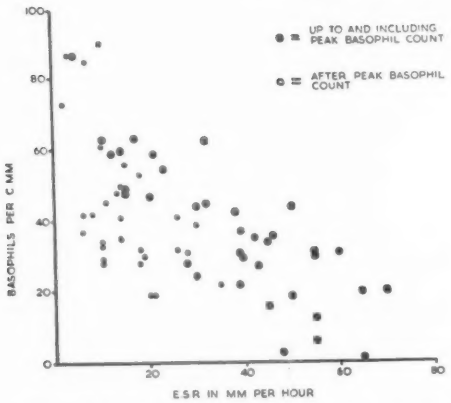

FIG. 3.—The relationship between the basophil count and the erythrocyte sedimentation rate in eight cases of acute rheumatism.

basophil count and the E.S.R. but this relationship ceased as the basophil count began to fall.

The ninth child with acute rheumatism was a boy of 9 years old who had a relapse during his illness and is therefore considered separately (Fig. 4, Case 20).

The basophil count was 25 per c.mm. on admission six days after the onset of symptoms. The pyrexia, leucocytosis and joint pains quickly subsided and after a few days the basophil count began to rise steadily, reaching 81 per c.mm. on the 17th day. During the same period the E.S.R. was gradually falling. At the end of the fourth week in hospital, however, there was a sudden recurrence of joint pains and pyrexia; the basophil count fell to 16 per c.mm. and the E.S.R. increased again. Salicylate dosage was increased, and the symptoms disappeared; the basophil count again began to rise, reaching 63 per c.mm. before levelling off at 50 per c.mm. Concurrently the E.S.R. fell to normal and the child thereafter made an uninterrupted recovery.

One further child with acute rheumatism who had no polyarthritis, and therefore did not fulfil the criteria, was nevertheless included in the study because she had severe carditis, subcutaneous nodules and a previous history of rheumatism so that the diagnosis could not be in doubt.

She was a girl of 11 years (Fig. 4, Case 21) who had had an acute attack of rheumatism two years previously from which she had made a good recovery. Five days before the first basophil count, she vomited and complained of abdominal pain. Pyrexia developed and on admission she was seriously ill with slight cyanosis, tachycardia, leucocytosis of 19,000 per c.mm., and an E.S.R. of 145 mm. in the first hour (Westergren). Subcutaneous nodules were palpable over the occipital region. Systolic and diastolic murmurs were audible at the heart apex and a radiograph of the chest showed considerable cardiac enlargement. The basophil count was 19 per c.mm. Treatment with salicylates and antibiotics resulted in some improvement; the E.S.R. after 10 days had fallen to 100 mm. per hour and the basophil count had risen to 55 per c.mm. During the next 14 days, however, the child's condition deteriorated, the apex beat moved out into the axilla, the E.S.R. rose again to 121 mm. per hour and the basophil count fell to 28 per c.mm. In view of this deterioration, treatment with cortisone was started; this resulted in disappearance of basophils from the peripheral blood and a fall in the E.S.R. to 10 mm. per hour, and coincided with clinical improvement. Two weeks after starting cortisone, however, she developed acute pharyngitis; the basophil count rose to 48 per c.mm. and the E.S.R. to 25 mm. per hour. With recovery, the basophil count again fell to a very low level, and the E.S.R. returned to normal. The dose of cortisone was gradually reduced, and when it was only 50 mg. per day, the basophil count began to rise, and the curve thereafter showed the gradual rise and fall with levelling off between 30 and 40 cells per c.mm., which has been demonstrated in recovery

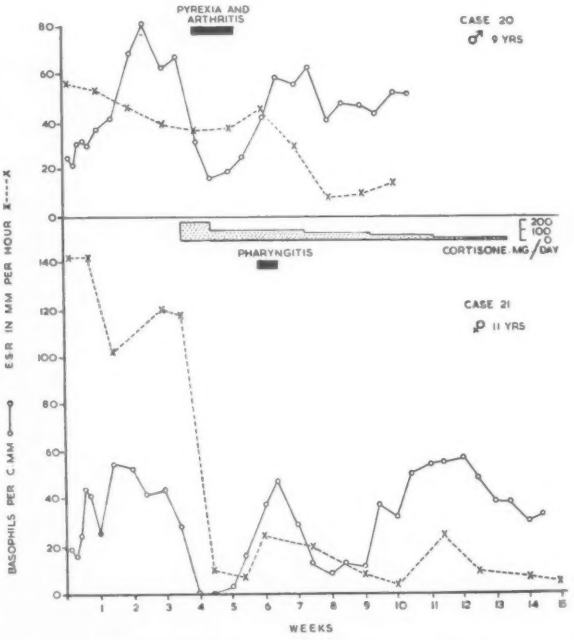

FIG. 4.—Serial basophil counts and erythrocyte sedimentation rates in two cases of acute rheumatism with complications.

from uncomplicated acute rheumatism. On reducing the dose of cortisone the E.S.R. showed a slight rise but quickly fell again to normal, and the child made a steady and uneventful recovery.

This case therefore illustrates a reversal of the usual inverse relationship between the basophil count and the E.S.R. as a result of the action of cortisone in reducing the E.S.R. and lowering the basophil count.

Anaphylactoid Purpura. Because of the variable course of the disease, the six children with anaphy-

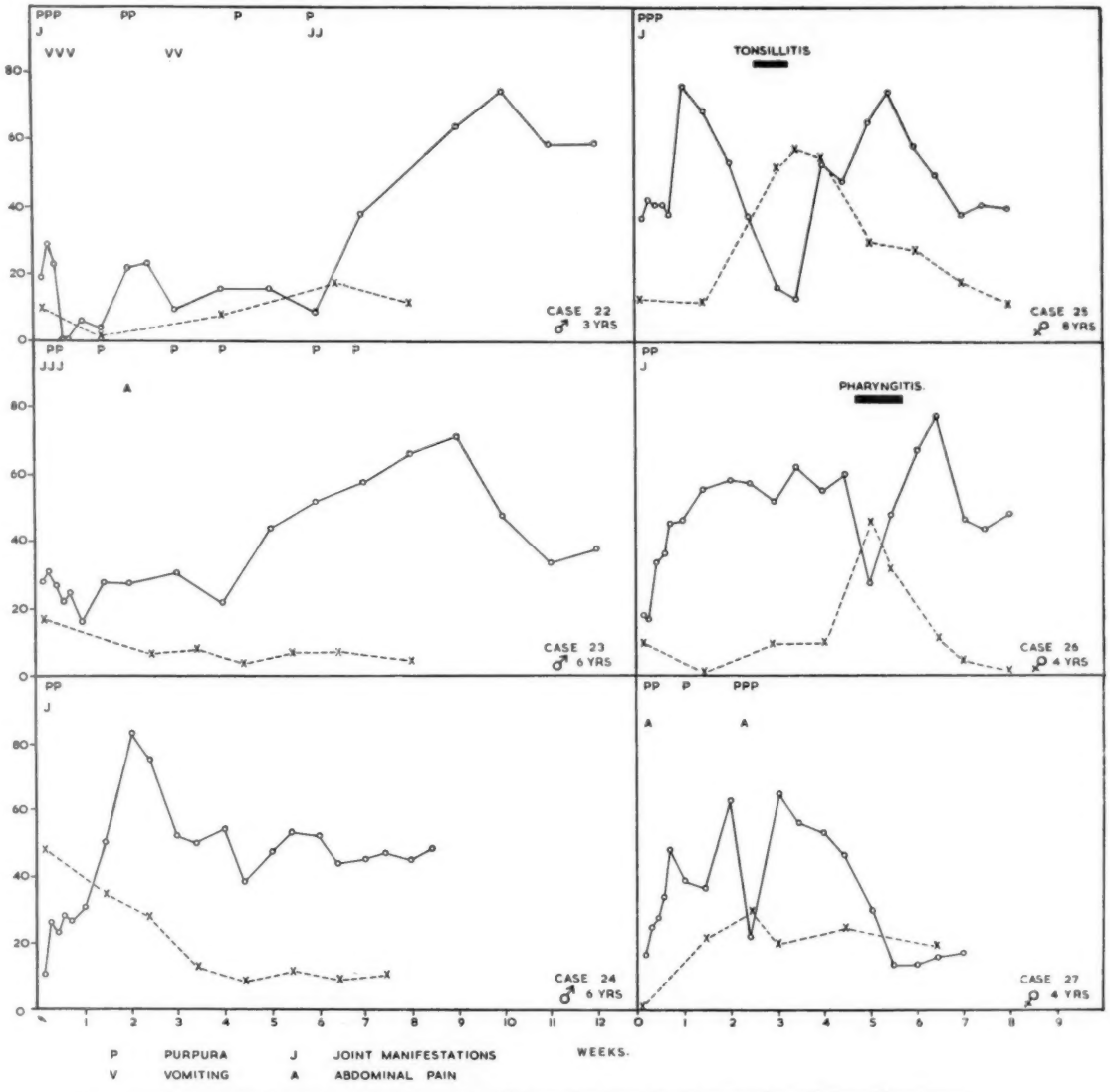

FIG. 5.—Serial basophil counts and erythrocyte sedimentation rates in six cases of anaphylactoid purpura.

lactoid purpura could not be treated as a single group for analysis of the results and the data for each child are therefore presented separately (Fig. 5).

In Case 22, the child was severely ill with vomiting and haematemesis, and fresh purpura continued to appear during the first six weeks. The basophil count remained low during this period, falling even lower during episodes of acute vomiting, and during a recrudescence of joint symptoms in the sixth week. With recovery the number of basophils increased steadily to a maximum count of 75 per c.mm. and then decreased a little and remained fairly stationary. Case 23 showed a similar series of events although the child was not so ill and recovery began about the fifth week. In spite of an uninterrupted clinical recovery this boy continued to have occasional slight purpura without any effect on the basophil count, which rose steadily to a maximum of 72 per c.mm. and then levelled off. In both Cases 22 and 23 the E.S.R. was low throughout the illness.

In Case 24 recovery was rapid and uninterrupted, with no further purpura or arthritis after the first few days. The basophil count rose rapidly from 11 per c.mm. on the day of admission to 83 per c.mm. at the end of two weeks and thereafter fell to about 45 per c.mm. The E.S.R. was high initially, possibly indicating a mild respiratory infection, and fell steadily as recovery progressed. Cases 25, 26 and 27 were each characterized by initial recovery, followed by a relapse or complication, succeeded again by recovery. In case 25 there were no

further manifestations of the disease after the first few days and the basophil count rose quickly to 76 per c.mm. During the third week it fell rather rapidly and acute tonsillitis developed with pyrexia and an elevated E.S.R. Treatment with penicillin resulted in subsidence of the fever and inflammation, followed by a fall in the E.S.R. and a rise in the basophil count to reach 75 per c.mm. once again. Thereafter the count fell gradually to level off at about 40 per c.mm. Case 26 showed a similar course of events with an initial rise of the basophil count to a level of about 60 per c.mm., and a rapid drop to 28 per c.mm. in the fifth week, coincident with an acute attack of pharyngitis associated with an elevated E.S.R. With recovery from the acute infection, the E.S.R. fell and the basophil count rose to a maximum of 78 per c.mm. before levelling off between 45 and 50 per c.mm.

In Case 27 there was abdominal pain with fresh purpura on admission, when the basophil count was found to be 17 per c.mm. After two days the symptoms subsided and the basophil count rose to 63 per c.mm. at the end of the second week. During the third week there was a fresh outbreak of purpura with further abdominal pain, and the basophil count fell sharply to 22 per c.mm. Thereafter recovery was uninterrupted, the basophil count rose again to 65 per c.mm. and then fell gradually to a level of about 15 per c.mm.

In spite of the variable course pursued in this disease, therefore, there is a pattern in the basophil response. The count is low in the acute stage, and rises during recovery. A relapse or an intercurrent infection is usually associated with an abrupt fall in the numbers of circulating basophils, which may be the first indication of such a setback.

In anaphylactoid purpura, the occurrence of purpura cannot always be correlated with the clinical condition, and fresh crops of purpura may appear from time to time long after apparent recovery. Similarly the basophil count could not be related to the occurrence of purpura, but reflected rather the general clinical state. It was particularly noticeable that an acute episode of haematemesis with shock could result in the immediate disappearance of circulating basophils, as in Case 22; whereas the number of basophils might steadily increase in spite of recurring purpura, as in Case 23. Only in Case 27 did the recurrence of purpura appear to be associated with an abrupt fall in the basophil count, but there was abdominal pain as well, indicating a more severe disturbance than purpura alone.

In general the eosinophil counts followed the trend of the basophil counts, in so far as the numbers of eosinophils diminished during episodes of acute illness and tended to increase in the recovery phase. The counts were, however, much more variable and sudden and unaccountable fluctuations often took place without coincident changes in the basophil count or the clinical state.

Discussion

Basophil Counts in Healthy Children. The difficulty of selecting normal children for leucocyte counts has been pointed out by Sturgis and Bethell (1943). Relatively mild infections, such as are common among apparently healthy school children, may cause fluctuations in the leucocyte count, while increased eosinophil and basophil counts have been reported in chronic tonsillar enlargement and chronic sinusitis respectively (Bunting, 1914; Rud, 1947). It was therefore decided to study healthy children in hospital rather than in the schools or at home, because a thorough clinical examination could be made which would ensure the absence of minor infections. For this reason the number of healthy children is small but may nevertheless present a more accurate standard of health than a cross-section of the school population. The preponderance of boys is due to the greater frequency of inguinal hernia in boys than in girls.

The numbers of basophils in the peripheral blood of these healthy children are similar to those found in the blood of adults by the method of Moore and James (1953). Thus the mean count of $45{\cdot}0 \pm 2{\cdot}5$ per c.mm. does not differ significantly from the mean counts of 46·7 per c.mm. found in 36 men by Moore and James, 41·0 per c.mm. in 30 men and women by Angeli, Tedeschi and Cavazzuti (1954), and $44{\cdot}8 \pm 2{\cdot}4$ per c.mm. in 96 men and women by Rorsman (1957a), while the range from 13 to 94 per c.mm. is similar to the ranges of 11 to 107 recorded by Moore and James and of 9·3 to 112·5 recorded by Angeli and his colleagues. After the characteristic rise and fall in the basophil count in the immediate newborn period (Mitchell, 1955) the count remains at the same level throughout childhood, an observation which confirms the work of Kato (1935). Neither Angeli and his colleagues nor Rorsman found significant sex differences in their series of basophil counts and similarly in the present study no difference between the counts in boys and girls was found. Although the number of children is too small to fix the extreme limits of normal, basophil counts below 10 per c.mm. or above 110 per c.mm. should be regarded as probably abnormal, although for any one individual the limits of normal may be very much narrower. It is apparent that the criteria suggested by Alder (1923), namely, that an increase or decrease of more than 15 cells from a mean value of 35 cells per c.mm. should be regarded as pathological, are far too limited.

Basophil Counts in Disease. The ill children to be studied were carefully selected in order to exclude

those who were only mildly ill or in whom the diagnosis was in doubt. Thus all the children included were moderately to severely ill and presented a 'textbook picture' of the disease concerned. This was considered to be important in determining the characteristic changes in the basophil count for each disease.

The results indicate that in the three acute diseases studied, the circulating basophils are scanty or absent during the acute phase, increase in number during recovery and are plentiful during the immediate convalescent phase of the illness. Similar changes occur in the numbers of eosinophils, a pattern of response to acute infection which is well established (Wolman, 1951; Weiner and Morkovin, 1952). With full clinical recovery the numbers of basophils return to normal levels; counts have not been continued long enough to determine whether further changes occur during the later stages of convalescence.

Basopenia. The finding of low basophil counts in the acute stages of disease is in accord with some of the earlier reports based on counts of basophils made from blood smears. Thus Arneth (1920) stated that basophils disappeared almost completely from the peripheral blood in influenza and Benjamin and Ward (1932) reported that, although individual counts were inaccurate by their method, there was generally a fall in the number of basophils during the febrile phase of measles, with a rise during convalescence amounting to basophilia during the second week. Whitby and Britton (1953) state that basophils may disappear altogether in acute infections. On the other hand Dible's textbook of pathology (1950) states that 'the proportion and number of basophil leucocytes in the blood are practically never affected by disease, if we except myeloid leukaemia and a slight increase in polycythaemia vera'.

There have been few reports based on accurate counting methods. Mallek (1955) and Labendzinski (1956) found low counts in some acute infectious diseases such as typhoid fever and bacillary dysentery, with a rise during recovery. Their technique involved the haemolysis of red cells and staining of basophils in a thick drop of blood, and was therefore an improvement on the older methods, but still lacked the precision of a counting chamber method. Rorsman (1957a), using a modification of the method of Moore and James (1953), found a mean basophil count of only 8·1±2·7 per c.mm. in 22 cases of urticaria; no such basopenia was found in cases of asthma (Rorsman, 1957b).

Low basophil counts in the present series were generally accompanied by eosinopenia, a characteristic phenomenon of stress. It seems reasonable therefore to attribute the diminution in the number of basophils to the stress of the acute disease, since it is an apparently non-specific reaction common to several diseases of varying aetiology. On this view, it might be expected that other forms of stress would also cause basopenia. Camerada and Leo (1955) have shown experimentally that thyroxin causes a decrease in the numbers of basophils as well as of eosinophils, although it must be said that these authors attributed the effect to a specific action of thyroxin. Fig. 6 shows the results of serial basophil counts on a boy of 10 years with hyperthyroidism and a girl of 20 months with hypothyroidism. The basophil count was low in the acutely thyrotoxic state and rose to normal levels on treatment with thiouracil, whereas the basophil count was abnormally high in the cretin, and fell to normal levels after treatment with thyroid was started, with the usual delay of 10 days or so in the response to this hormone. These illustrative cases lend support to the view that the low basophil counts observed in acute disease are the result of non-specific stress. If such is the case cortisone should cause a disappearance of the basophils from the circulating blood stream, as it does with eosinophils, and this effect has in fact been demonstrated (Code, Mitchell and Kennedy, 1954). It might be argued that the very low basophil counts found in urticaria by Rorsman (1957a) were due to stress, but here the situation is rather different because urticaria is common to a heterogeneous collection of conditions in many of which there is evidence of disordered histamine metabolism (Rose, 1941; Adam, Hunter and Kinnear, 1950). Rorsman's patients had no general systemic disturbance so that the very low counts observed are more likely to have been peculiar to urticaria and not the result of a non-specific stimulus.

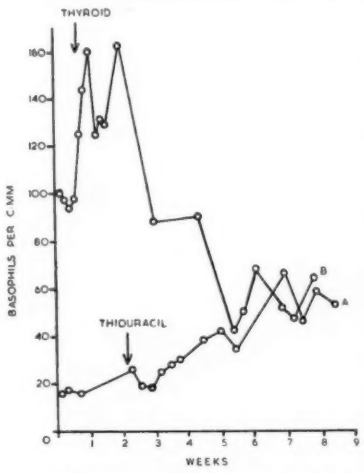

FIG. 6.—Serial basophil counts in (A) a boy with hyperthyroidism treated with thiouracil and (B) a girl with hypothyroidism treated with thyroid extract.

Basophilia. The present work indicates that there

are increased numbers of circulating basophils during the phase of recovery from an acute disease. Increases in the numbers of basophils are more readily observed by differential counts from blood smears than decreases, and therefore although earlier reports on the incidence of low basophil counts were often uncertain and conflicting, there is a larger and to some extent more reliable collection of evidence that the basophil count may be increased in certain diseases. Thus it is established that there may be very considerable numbers of circulating basophils in leukaemia and in polycythaemia (Ehrlich, 1891; Alder, 1923; Doan and Reinhart, 1941). Although extremely high counts have been recorded in leukaemia, even as high as 163,000 basophils per c.mm. (Joachim, 1906), the highest count so far recorded by the present writer was 237 basophils per c.mm. in a boy of 3 years with acute leukaemia, who had 400,000 leucocytes and 419 eosinophils per c.mm. When the total leucocyte count fell to 30,400 per c.mm. one week after starting treatment with mercaptopurine, the basophils fell to 17 per c.mm. and the eosinophils to 25 per c.mm., while at two weeks the leucocyte count was 4,800 per c.mm. the basophils were 9 per c.mm. and the eosinophils had disappeared completely. This suggests that mercaptopurine may have a greater effect than irradiation on the basophils in leukaemia, since there is evidence that these cells are resistant to radioactive agents (Doan and Reinhart, 1941; Johansen, 1955), with the possible exception of radioactive phosphorus (Turchini and Kein, 1955).

Apart from these diseases of the blood-forming organs, an increase in the number of circulating basophils has been reported in other blood diseases, such as chronic haemolytic anaemia and chlorosis (Alder, 1923), and in diseases of the skin (Canon, 1892; Klausner and Kreibich, 1913). Bunting (1914) reported that the basophils are increased in early Hodgkin's disease, but thought that this might be due to chronic sinusitis, which according to this author is constantly associated with an increased number of basophils. Graham (1920) reported increased numbers of basophils in a patient infected with hookworms. Nevertheless, as recently as 1951, Muir's *Textbook of Pathology* observed that 'there is no condition known which regularly calls forth a basophil leucocytosis'.

Bigart (1902) and Rubinato (1907) reported that in cirrhosis of the liver there were greatly increased numbers of circulating basophils, amounting to as much as 20·6% of the total leucocyte count in one case, an observation of some interest since high levels of blood histamine have recently been recorded in this disease (Mitchell, Butt and Code, 1954).

As with the initial basopenia, the basophilia during recovery from acute disease cannot at present be related to any function of the basophils, but is probably a non-specific response to the earlier stress.

Clinical Value of Basophil Counts. The eosinophil count is of some use as a guide to progress in an acute infection (Hain, 1951; Whitby and Britton, 1953), and the greater consistency of the basophil count suggests that it might be of even greater value. Moreover, the demonstrated relationship between the basophil count and the E.S.R. indicates a possible use for the basophil count in the prognosis of acute rheumatism, since a steady increase in the number of circulating basophils has the same significance as a steadily falling E.S.R. Unfortunately the limiting factor is the wide range of normal values, compared with the small range of normal for the E.S.R. The basophil count is remarkably constant in the healthy individual but the normal level is not usually known when a patient is seen in the acutely ill stage. Occasionally the basophil count performed daily has proved of value, when a sudden fall in the number of basophils has been the first indication of a relapse, preceding clinical manifestations by a day or more. Nevertheless increasing experience of basophil counts in a variety of clinical conditions indicates that not enough is known about the factors which may influence the count to permit its use as a reliable clinical test at present.

Functions of the Basophil. In the early years of this century there was much discussion on the relationship of the basophils (mast cells of the blood) to the mast cells of the tissues, but by the late thirties enough information had accumulated to enable Michels (1938) to state that 'in mammals the two types have nothing in common save the basophilic metachromatic staining granules'. This statement must be modified today, since the tissue mast cells, like the basophils, contain both heparin and histamine (Jorpes, 1946; Riley and West, 1953). Nevertheless, the balance of evidence still favours the view that the two types of cell are distinct.

At various times the basophils have been regarded as degenerating lymphocytes, as unripe eosinophils, and even as 'a vestigial remain analogous with the appendix' (Phillips, 1953), but they are now generally accepted as mature granulocytes fully equivalent to the eosinophils and neutrophils (Michels, 1938). There may, however, be a functional relationship between basophils and eosinophils, since they have certain properties in common such as their response to stress or to cortisone (Code *et al.*, 1954; Hamerston, Elveback, Halberg and Gully, 1956). Moreover, there is evidence that while basophils are the

main reservoir of histamine in the blood, the eosinophils also sometimes carry histamine, providing additional histamine-carrying capacity which is readily available when the occasion arises (Code and Mitchell, 1957).

It seems reasonable to assume that the content of such potent substances as heparin and histamine bears some relationship to the function of the basophil, although there may be other, possibly more fundamental, activities. Tötterman (1948) searched for evidence of an increased tendency to haemorrhage when increased numbers of basophils were present in the peripheral blood, but was unable to demonstrate that such basophilia predisposed to bleeding. This is perhaps not surprising, since Angeli and his colleagues (1955) showed experimentally that the intravenous injection of heparin caused an increase in the number of circulating basophils, and that the period of maximum augmentation of the basophil count coincided with the most rapid diminution in anti-coagulant activity of the injected heparin, an effect which they attributed to a specific regulatory action of the basophils. Wintrobe (1951) considered that basophils might function in inflammation by delivering anticoagulants to facilitate absorption or to prevent clotting of blood and lymph in the obstructed tissue. The chemical studies of Turchini and Kien (1955) led them to believe that in the presence of disease the synthesis of heparin in the basophils is disturbed so that precursor substances are liberated which are necessary for the elimination of toxic products.

As far as histamine is concerned, Graham and her colleagues (1955) suggested that the basophils may be a source of a limited amount of the amine which is immediately available wherever needed to tide over the period before the arrival of more adequate supplies from the tissue mast cells. It is possible, on the other hand, that the basophils are simply a safe means of transporting a potentially toxic substance pending its destruction or excretion.

It is apparent that in spite of recent progress we are still a long way from answering what Riley (1954) has called the 'riddle of the mast cells', and the answer is unlikely to be found until the larger problems of the physiological significance of heparin and histamine in the body have been solved.

Summary

The circulating basophils have been counted in 67 healthy children and in 27 acutely ill children throughout the course of their illness.

The counts in healthy children were not significantly different from those found in adults by other authors, and the mean count did not vary significantly throughout childhood.

In the three acute diseases studied, lobar pneumonia, acute rheumatism, and anaphylactoid purpura, the number of circulating basophils was always low in the acute stage and high during the stage of recovery. These are regarded as non-specific changes in response to the stress of the acute disease.

Serial basophil counts give some indication of the progress of the disease but are not sufficiently reliable to be of practical clinical use at present.

Possible functions of the basophils are discussed.

I am grateful to Professor J. L. Henderson for his encouragement and criticism.

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INTRAPERITONEAL BLOOD TRANSFUSION IN CHILDREN IN ACCRA WITH SPECIAL REFERENCE TO THE TREATMENT OF KWASHIORKOR

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 11, 1957)

The giving of blood to small children presents particular difficulties to medical practitioners in West Africa. Equipment is often inadequate and the time required to ensure the success of the transfusion can often be ill-spared from numerous other hospital and out-patient duties. In addition, the children are usually ill-nourished and dehydrated and intravenous therapy is a major undertaking to those unpractised in paediatric techniques. Waite, Colucci and Glaser (1956) recorded the successful transfusion of blood by the intraperitoneal route in young children and this appears to be a simple and rapid procedure which, if successful, would be of the greatest benefit to practitioners and their young patients in West Africa. This method has been used in Accra and, to date, 43 intraperitoneal blood transfusions have been given to 36 children with clinically satisfactory results. In this paper the methods utilized are outlined and the results briefly discussed. Details of 15 transfusions which have been given to 11 malnourished babies are given.

Methods

The majority of the children were suffering from marasmus, marasmic kwashiorkor or kwashiorkor. Intercurrent infection and multiple infestations were common. The patients with florid signs of kwashiorkor with oedema were treated with skimmed milk alone or skimmed milk with soya bean flour and/or fish until the oedema disappeared (the child then looking the picture of marasmic kwashiorkor) before transfusion was given.

The usual routine in saline and albumin grouping and compatibility tests was followed and the results confirmed by an indirect Coombs test. All the children were rhesus positive (anti-D). In Accra the incidence of the sickle-cell and haemoglobin C traits is in the region of 19% and 10% respectively and the blood with these traits is normally stored and utilized by the transfusion service (Edington, 1956). It was not, however, employed for intraperitoneal transfusions excluding one instance in which S trait blood was given intraperitoneally to one sickling negative baby and the subsequent appearance of the sickling positive cells in the peripheral circulation was studied.

The patients were prepared as for paracentesis abdominis. (In Ghana special care has to be taken in the examination of the liver, spleen and bladder.) The patient was propped up and the abdominal wall and peritoneum 2 inches below and lateral to the umbilicus was anaesthetized with 1% novocaine. The usual routine giving set with a 20-gauge needle was employed and the blood allowed to drip through the set before the needle was inserted into the peritoneal cavity. The amount usually given was 20 ml. per lb. body weight and the rate of flow was regulated to 30 drops per minute. A cover of penicillin was given during the transfusion and sedation when required. Following transfusion a course of antimalarial therapy was prescribed to obviate the possibility of transmitting malaria.

Results

Three of the 39 children transfused died. The minimum period between transfusion and death was two days and the maximum 20 weeks. In no instance was the transfusion thought to be implicated in the cause of death. Necropsies were performed on all three children. A child suffering from severe marasmus died two days after transfusion. Necropsy revealed the cause of death to be marasmus and bronchopneumonia. The free blood in the peritoneal cavity was fluid and uninfected and no adhesions were noted. Haemolysis had not occurred. A second child, an orphan, aged 4 months and weighing only 4 lb. 10 oz., had been fed entirely on maize gruel from the age of 2 days. Death

occurred 12 weeks after the transfusion and a necropsy established that the cause was hydronephrosis, pyelonephritis, interstitial pneumonitis and malnutrition. The peritoneal cavity contained a few black specks in the paracolic gutter but was otherwise normal. A third child died 20 weeks after transfusion. The peritoneal cavity was free from infection and adhesions.

From the results of these necropsies it would appear that the introduction of compatible blood into the peritoneal cavity is unlikely to lead to complications in later life.

The infants in general withstood the procedure well: only one severe reaction occurred and that was in the sickling negative infant who received sickling positive blood. The complications observed after transfusion were abdominal distension in 27 cases (this was usually mild, gave no cause for anxiety and cleared up within 48 hours), mild pyrexia in 26 cases, and one abdominal haematoma which resolved spontaneously. There were no cases with melaena, bowel symptoms or jaundice.

The sickle-cell negative patient who received compatible sickling positive blood (20 ml. per lb. body weight) showed the most severe reaction—the temperature rose to 102·8° F. and vomiting, restlessness and abdominal distension occurred. These symptoms regressed spontaneously at the end of four days. The eventual response to transfusion in this patient was considered, however, to be eminently satisfactory. The rate of appearance of the sickling positive cells in the peripheral blood of the patient was studied and the results are shown in Table 1.

TABLE 1

PERCENTAGE OF SICKLING POSITIVE CELLS (S) APPEARING IN PERIPHERAL BLOOD OF NON-SICKLING INFANT

Day*	S Cells	Day*	S Cells	Day*	S Cells
	%		%		%
1	Scanty	49	9	70	0·2
2	Scanty	53	8	71	0·1
4	1	56	8	73	0·5
9	4	58	7	73	Scanty
21	15	60	5	74	Nil
28	12	69	1	75	Nil

* Day following transfusion.

From Table 1 it appears that, following intraperitoneal blood transfusion, the transfused cells reach their greatest concentration in the peripheral blood two to four weeks after transfusion. No sickling positive cells were detected in the peripheral blood at the end of 74 days. No explanation can be given for this. The recipient did not appear to be suffering from a haemolytic anaemia and, as the average life of the erythrocyte is 120 days and as sickle-cell trait cells are known to survive normally, it was expected that the sickled cells would be detected for a longer period.

The clinical response of the patients to blood

TABLE 2

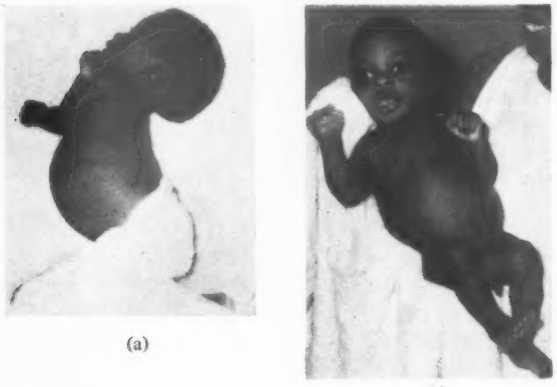
CLINICAL DETAILS OF 11 BABIES SUFFERING FROM SEVERE MALNUTRITION TREATED BY INTRAPERITONEAL BLOOD TRANSFUSIONS

Case No.	Age (months)	Weight on day of Transfusion (lb.)	(oz.)	Condition	Hb. before Transfusion (%)	Hb. after Transfusion (%)	Result	Remarks
1	8	9	4	(Failure to thrive) Marasmus	60	85	Discharged	
2	4½	5	4	Marasmus	57	70	Died after 12 weeks	
3	14	11	3	Marasmic kwashiorkor	40* 65	60 78	Discharged	Slow progress
4	12	11	0	Marasmic kwashiorkor	55	83	Discharged	
5	5	7	2	(Failure to thrive) Marasmus	45 60	67 90	Discharged	Attack of malaria before 2nd transfusion
6	9	8	1	Marasmus	53	75	Discharged	
7	44½	22	11	Marasmic kwashiorkor	55	79	Discharged	
8	12	10	2½	Kwashiorkor	44	67	Discharged	
9	30 T	11	1	Kwashiorkor	55	71	Discharged	
10	18	13	0	Marasmic kwashiorkor	50 63	70 81	Died 20 weeks after transfusion	Two attacks of malaria before 2nd transfusion
11	about 10	9	1	Kwashiorkor	45 69	68 80	Discharged	Slow progress

* Where two figures appear under haemoglobin before and after transfusion, the top figure refers to the first transfusion and the lower figure to the second transfusion.

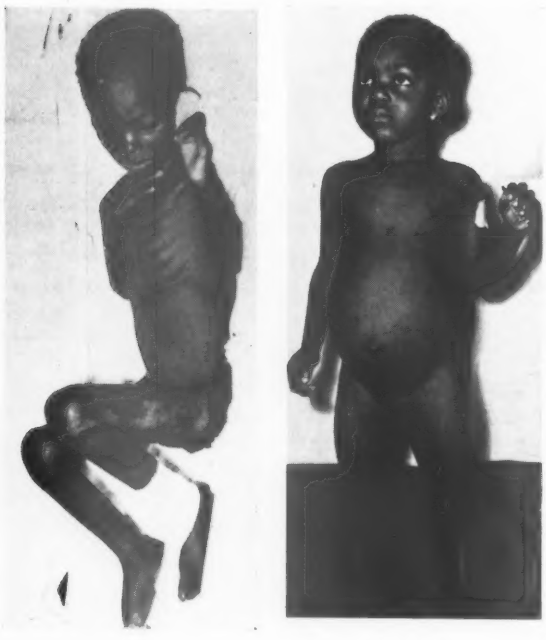
transfusion was good. Brief details of 11 severely malnourished patients who had received 15 transfusions are given in Table 2.

It is difficult to assess the results of treatment in kwashiorkor, and controlled studies were not possible. Clinically, however, the babies appeared to benefit immensely from the transfusion (Figs. 1 and 2) and, perhaps most important, the nursing staff were most enthusiastic about it as a method of treatment. Not only did the transfusion increase the haemoglobin level of the blood but it appeared to increase the child's resistance to intercurrent infection, the incidence of which, especially of staphylococcal infection, was lower in these children. The rate of recovery was also usually greatly accelerated. Four patients, however, showed a comparatively slow response and in these cases transfusion was repeated in six weeks when a rapid recovery ensued.



(a) (b)

FIG. 1.—Case 5. Boy aged 5 months, (*a*) before treatment: marasmus; weight 7 lb. 2 oz. and (*b*) after treatment.



(a) (b)

FIG. 2.—Case 7. Girl aged 44½ months, (*a*) before treatment: marasmic kwashiorkor; weight 22 lb. 11 oz. and (*b*) after treatment.

Comment

In the malnutritional syndromes seen in Accra the most important single factor lacking in the diet is protein and it would appear that the giving of blood is a simple and rapid method of remedying this deficiency. Hitherto blood has not been used in the treatment of marasmus and kwashiorkor in Accra in view of the technical difficulties involved, and also because it is only recently that blood has become readily available for transfusion. The intraperitoneal transfusion provides a simple and safe method of giving blood to these patients. Clinically the infants have responded well to this form of therapy. It is regrettable that full biochemical investigations could not be undertaken in each case but time and staff were lacking and it is hoped that in the future a more intensive investigation can be done. Meanwhile, however, it has been shown that intraperitoneal blood transfusion is a useful and simple therapeutic measure in West Africa.

Summary

Intraperitoneal blood transfusion has been found to be a safe and simple method of treatment. Erythrocytes are absorbed from the peritoneal cavity into the peripheral circulation. Abdominal complications are unlikely to occur in later life.

My thanks are due to the Chief Medical Officer, Ghana, for permission to publish, to Dr. G. M. Edington for advice and details of the necropsies, to the nursing staff of the Princess Marie Louise Hospital and to the staff of the Medical Research Institute, particularly Mr. Sackey.

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TRAUMATIC SUBPERIOSTEAL HAEMATOMA OF THE FEMUR IN THE NEWBORN

BY

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(RECEIVED FOR PUBLICATION DECEMBER 2, 1957)

Subperiosteal haemorrhage usually accompanies fracture of a long bone at birth. The occurrence at birth of a subperiosteal haematoma without fracture was not widely recognized until attention was drawn to the condition by Snedecor, Knapp and Wilson (1935), who called it 'traumatic ossifying periostitis'. A few other reports of this type of birth injury were subsequently published under such titles as periosteal stripping (Burman and Langsam, 1939), neonatal contusion (Caffey, 1945) and ossifying haematoma (Brailsford, 1948), and the subject was later reviewed by Snedecor and Wilson (1949). The number of reported cases is still small, and no pathological studies have yet been published; we therefore present two cases, one of which was examined at necropsy.

Case Reports

Case 1 (M.H. 52/343). A first-born female child was born at term, her weight being 7 lb. 10 oz. (3·5 Kg.). She presented as a frank breech in the left sacro-anterior position. To effect delivery the left leg was brought down with some difficulty, the right following more easily. The baby appeared normal at birth but on the third day it was noted that she was not moving the left leg as freely as the right and that there was slight pitting oedema of the left foot. On the following day the distal end of the left femoral shaft was tender and felt thicker than normal. The infant's general condition was good and radiographic examination of the affected femur revealed no abnormality. (Fig. 1). At one week the thickening of the femur was more pronounced and there was radiological evidence of subperiosteal 'ossification' around the shaft which gradually increased (Figs. 2 to 5). The infant's general progress was quite satisfactory and she was discharged from hospital on the thirteenth day. At the age of 16 months radiological examination of the femur showed no abnormality (Fig. 6).

Case 2 (D.R.I. 54/274). A female infant weighing 8 lb. (3·6 Kg.) was born at term, the pregnancy being the mother's eighth. The mother was admitted in labour, with the infant presenting as a transverse lie, the arm having prolapsed into the vagina. Internal version was carried out with some difficulty and was followed by breech extraction. Following delivery the infant's condition was poor and she was kept in oxygen for 24 hours. During the first few days she was lethargic and fed slowly. It was noted that she was not moving her legs, and examination indicated that there had been severe injury to the spinal cord: there was slight costal indrawing, a patulous anus through which meconium constantly dribbled, and flaccid paralysis of both legs, though strong stimulation resulted in a withdrawal reflex. Radiological examination of the legs on the fourth day showed no evidence of injury to the bones (Fig. 7).

Towards the end of the first week pitting oedema of both legs developed and on the eighth day she was admitted to a paediatric ward in Dundee Royal Infirmary where the clinical findings were confirmed. By the end of the second week the oedema had diminished and there was now slight thickening of the distal end of the right femoral shaft. Radiological examination showed an opacity round the cortex of the femur, and this subsequently increased in size and density (Figs. 8 to 10). The oedema of the legs had completely disappeared when the infant was 3 weeks old although there was no appreciable diminution of the paralysis. Despite the severity of the birth injuries the infant fed well and seemed contented. An unexplained pyrexia developed at the age of 3 weeks. It was not associated with a leucocytosis and the blood was sterile on culture; radiological examination showed a small patch of atelectasis at the apex of the right lung. Intermittent pyrexia up to 105° F. continued for five weeks despite treatment with streptomycin and chlortetracycline, but the infant gained weight steadily, began to take notice and made slight spontaneous movements of the legs. The intermittent pyrexia subsided at the age of 8 weeks, but in the meantime costal indrawing had increased, and 10 days later the infant suddenly died from respiratory failure.

SUMMARY OF NECROPSY. The spinal cord showed gross destruction from approximately C 7 to T 3. The damaged segments were shrunken and stained with altered blood pigment. The lungs showed hypostatic congestion and oedema; the major intra-pulmonary bronchi contained mucopus and much of the right lung was collapsed. The other organs showed no abnormality

Figures 1 to 6. Serial radiographs of the left knee in Case 1.

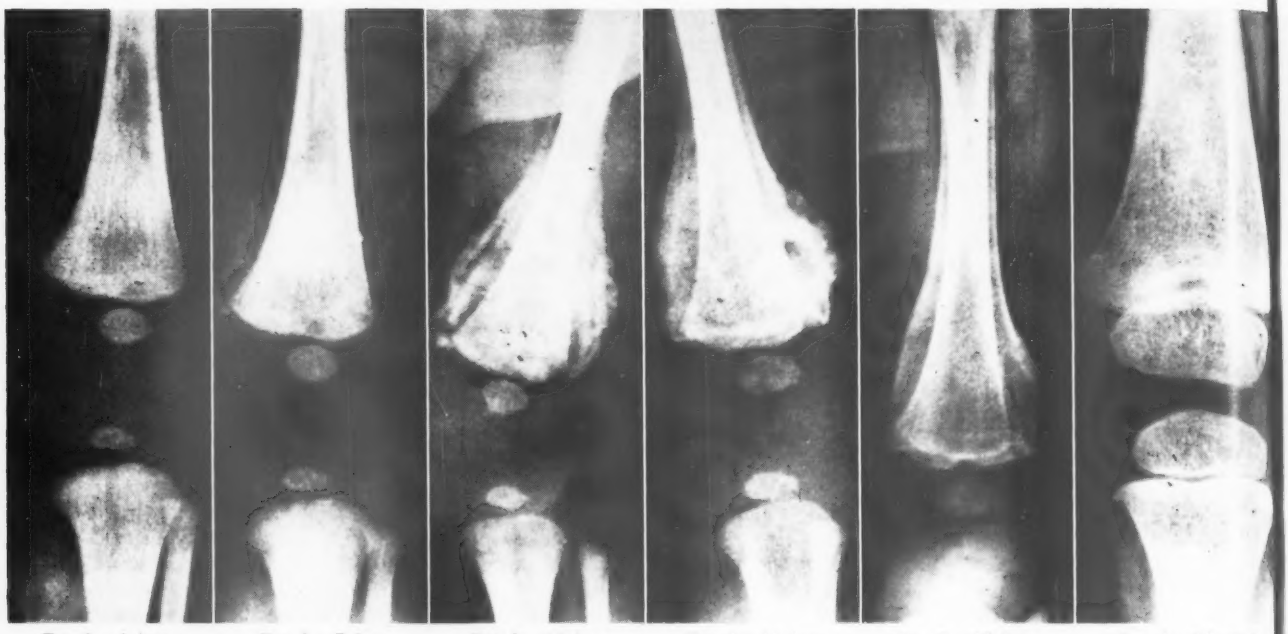

FIG. 1.—4 days. FIG. 2.—7 days. FIG. 3.—14 days. FIG. 4.—21 days. FIG. 5.—35 days. FIG. 6.—16 months

FIG. 1.—No abnormality visible on fourth day after birth.

FIGS. 2-5.—Appearance and subsequent increase of subperiosteal ossification round lower end of femur.

FIG. 6.—At 16 months the ossified haematoma has disappeared completely and femur appears normal.

on macroscopic and histological examination. The right femur which showed no gross abnormality was removed and examined histologically.

HISTOLOGY OF RIGHT FEMUR. Transverse sections of the distal part of the shaft (Figs. 11 and 12) showed that part of the surface was covered by a layer of new subperiosteal bone which was less sclerotic than the original cortex. The new bone enclosed a relatively large space, surrounded by scar tissue and filled with degenerated blood and fibrin and fragments of dead bone but these had not excited any osteoclastic activity. The scar tissue contained many histiocytes laden with haemosiderin but showed no evidence of pyogenic inflammation. The cortex of the original shaft appeared to be thinner beneath the new layer than it was elsewhere but showed no other abnormality.

Discussion

Clinical Features. Subperiosteal haematoma of a long bone in a newborn infant is almost invariably the result of trauma during birth. It should be suspected when there is a history of difficult delivery, particularly if internal version has been performed, and there is limitation of movement of a limb, possibly pain on passive movement, and swelling of soft tissue. Careful palpation will usually reveal tender thickening around the affected bone. At this stage, radiological examination may show the soft tissue swelling but will probably reveal no bony abnormality. However, the diagnosis will be confirmed by the radiological changes which appear after the first week (Figs. 1-10). In the absence of clinical signs of injury, minor degrees of subperiosteal haemorrhage may easily be overlooked; thus, Snedecor and Wilson (1949) found evidence of the condition in no less than three of 50 consecutive breech deliveries when routine radiographs of the limbs were taken on the 7th day of life. In their experience the distal end of the femur is most commonly involved although the proximal end and the tibia may be affected. Involvement of the humerus has also been reported, usually when delivery has been by the vertex (Scaglietti, 1938).

Injury to the epiphysis is quite commonly associated with subperiosteal haematoma but was not present in either of our cases. Both lesions occurred together in two of the 11 cases of injury to the long bones at birth reported by Snedecor and Wilson (1949) while four had epiphyseal damage alone.

Pathogenesis. Subperiosteal haemorrhage is probably produced by manual traction on a limb combined with torsion (Snedecor *et al.*, 1935) and hence

Figures 7 to 10.—Serial radiographs of the right femur in Case 2.

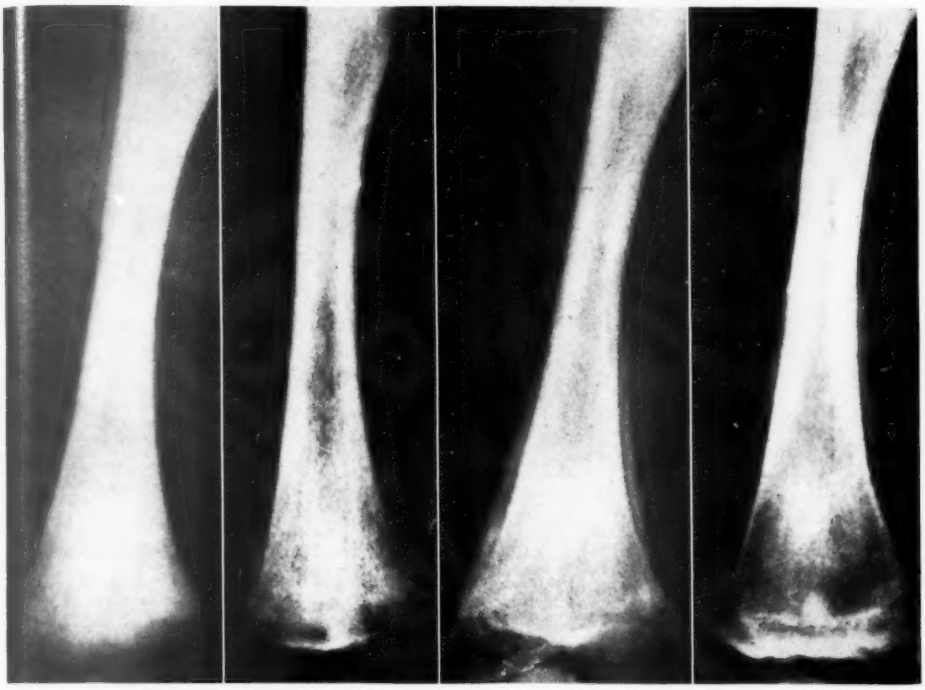

FIG. 7.—4 days. FIG. 8.—17 days. FIG. 9.—22 days. FIG. 10.—32 days.

FIG. 7.—No abnormality visible on fourth day after birth.

FIGS. 8-10.—Appearance and subsequent increase of ossification in subperiosteal haematoma.

(The opacity immediately above the epiphyseal centre in Fig. 9 is an artefact.)

is most likely to occur in a difficult internal version and in an assisted breech delivery.

Stripping of the periosteum from the shaft of a long bone is believed to occur much more easily in the foetus and newborn than in the adult (Macewen, 1912; Caffey, 1945). This impression appears to have been confirmed by investigation at necropsy (Barmeyer, Alderson and Cox, 1951) and it is therefore reasonable to assume that forcible periosteal stripping during delivery injures or tears the numerous blood vessels that are known to enter the bony cortex from the periosteal layer (Ham, 1953) giving rise to a subperiosteal haematoma which is presumably followed by the formation of callus and new subperiosteal bone. This belief is supported by the histological findings in Case 2, particularly by the evidence that bleeding had occurred at the site of the new subperiosteal bone. However, the presence of fragments of dead bone within this new subperiosteal layer indicates that bone injury, albeit of minor degree, has accompanied periosteal stripping and various possible explanations for this have obviously to be considered. A gross fracture of the shaft can reasonably be excluded, and we believe that direct manual compression during obstetrical manipulation is unlikely to cause necrosis of the dense cortical bone of the femoral shaft in a mature infant, though it might crush the more delicate trabeculae, many of them radially arranged (Ham, 1953), of immature cortical bone. The most probable explanation is that periosteal stripping was accompanied by avulsion of fragments of cortical bone as well as by subperiosteal haemorrhage, for our investigations at necropsy in the newborn have shown that the periosteum of the femur, though easily stripped from most of the shaft, is more firmly attached to the metaphysis and is inseparable from the bone and its muscle attachments along the linea aspera. It is also possible, of course, that devitalization of cortical bone follows injury to its blood supply from the periosteum (Ham, 1953). Avulsion of bone appears to have been regarded by Caffey (1956) as the explanation of 'chip fractures' accompanying new subperiosteal bone formation in relation to the tibia of an infant aged 3 weeks.

Differential Diagnosis. A presumptive diagnosis of subperiosteal haematoma may reasonably be made when clinical evidence of injury to a long bone is found after a difficult delivery, and is followed by the appearance and subsequent regression of the characteristic radiological changes. When these changes are slight, they may be confused with the double contour of the long bones that is sometimes seen in normal infants; the latter, however, is seldom visible during the first month of life and occurs

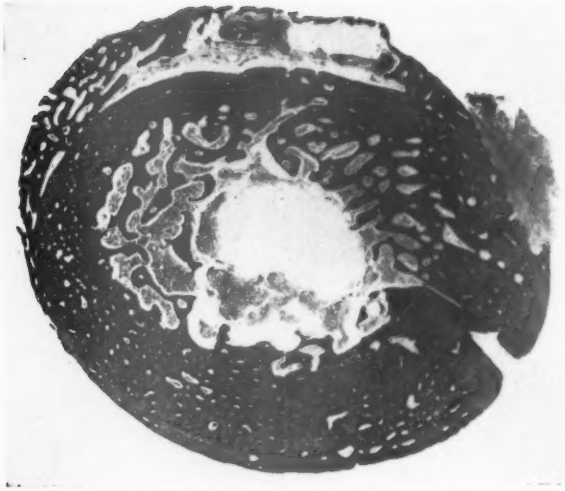

FIG. 11.—Case 2: Histology of femur. Transverse section of shaft showing layer of new subperiosteal bone on part of surface. A space within the new bone is filled with bone debris and altered blood. (Some of this debris has fallen out of the section during preparation.) H. and E. × 11.

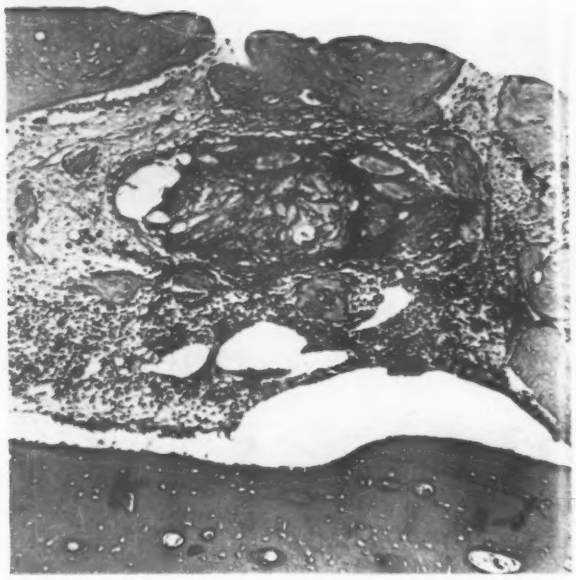

FIG. 12.—Case 2: Histology of femur. New subperiosteal bone under higher magnification showing mixture of necrotic bone and blood enclosed by new trabeculae. H. and E. × 70.

most frequently in small premature infants, usually after a normal birth (Glaser, 1949; Hancox, Hay, Holden, Moss and Whitehead, 1951). Infantile cortical hyperostosis also gives a somewhat similar radiological picture and at one time Smyth, Potter and Silverman (1946) even doubted the existence of ossifying subperiosteal haematoma as a separate entity, believing that the cases so diagnosed were really examples of infantile cortical hyperostosis. In the latter condition, however, there is considerable systemic disturbance with pronounced irritability, loss of weight and fever, several of the long bones are usually involved throughout their entire length, and, characteristically, the mandible and clavicles are affected (Fairbank, 1952). Furthermore, infantile cortical hyperostosis rarely occurs during the first 2 weeks of life although Kitchin (1951) has reported one rather atypical case in a newborn infant, and the condition has been diagnosed radiologically *in utero* (Barba and Freriks, 1953; Bennett and Nelson, 1953). In the second of our two cases of subperiosteal haematoma, prolonged fever suggested yet another possibility, namely, osteomyelitis, but this diagnosis was rejected because ossification preceded the onset of fever, and study of the femur at necropsy showed no evidence of pyogenic inflammation.

When an ossifying subperiosteal haematoma is discovered some weeks or even months after birth, it may be mistaken for a sarcoma or for a manifestation of scurvy (Brailsford, 1948, 1953). Although scurvy may produce an indistinguishable radiological picture, it is usually accompanied by other signs of vitamin C deficiency, and in the absence of these a history of a difficult breech delivery will suggest a presumptive diagnosis of traumatic subperiosteal haemorrhage. It is theoretically possible, of course, that vitamin C deficiency might be a contributory factor in the pathogenesis of subperiosteal haemorrhage following birth trauma, but the mere fact that the haematoma undergoes 'complete resolution' when vitamin C is administered is not proof, as Brailsford (1953) avers, that scurvy has been partly responsible. Neither of the infants we have described showed any sign of vitamin C deficiency and, in the absence of corroborative evidence, it seems unnecessary to invoke scurvy as an additional aetiological factor in the neonatal period. Neither hypervitaminosis A nor syphilis is likely to be confused with subperiosteal haematoma, and both should readily be differentiated by the history and by full clinical investigation. Finally, subperiosteal haematomata may follow comparatively minor injuries in postnatal life and again this is presumably because the periosteum is more loosely attached to the bones than it is in adult life (Barmeyer, Alderson and Cox, 1951; Silverman, 1953; Bakwin, 1956).

Treatment. Subperiosteal haematoma of the newborn requires no treatment. As the bone

increases in diameter the subperiosteal layer becomes incorporated in the shaft and the bone eventually assumes its normal contour, though residual thickening may be visible radiologically for many months (Caffey, 1945). However, when there is an associated injury of the epiphysis, orthopaedic treatment may be necessary to prevent permanent disability.

Summary

The clinical and radiological features of traumatic subperiosteal haematoma of the femur in two newborn infants have been described.

In both cases there was a history of difficult breech delivery, with strong manual traction on one of the legs.

Necropsy was performed on one of the infants and examination of the femur showed a layer of new subperiosteal bone enclosing fragments of dead bone and some altered blood.

It is suggested that the subperiosteal haemorrhage was produced by a combination of manual traction and torsion of the limb and that cortical bone was probably avulsed as the periosteum was stripped off the femoral shaft.

The differential diagnosis and treatment have been discussed.

We wish to express our thanks to Professor J. L. Henderson and Professor A. C. Lendrum for their helpful criticism, to Dr. H. G. Morgan who performed the necropsy in Case 2, and to Mr. R. Fawkes for the histological preparations and photomicrographs.

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SUBGLOTTIC HAEMANGIOMA: TWO INFANTS WITH LARYNGEAL STRIDOR

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 24, 1957)

The literature contains records of 18 infants with stridor due to haemangiomata in or just below the larynx. Two of these were reported by Mr. James Crooks in this Journal (Crooks, 1954). Since then he has had three further cases at The Hospital for Sick Children, Great Ormond Street, and I am indebted to him for permission to publish details of two of them, bringing the total number of cases recorded up to 21.

Case Histories

Case 1. (Fig. 1). C.E. was a girl born on January 6, 1956. Laryngeal stridor developed after an attack of acute bronchitis at 6 weeks of age. The stridor continued with intermittent pyrexia, and a laryngoscopy was performed at another hospital when she was 3 months old. The larynx was found to be very red; no web or tumour was seen. The stridor continued despite antibiotics and a month later she was transferred to The Hospital for Sick Children. On examination there was biphasic stridor with rib and suprasternal recession. The child had a good colour and was not distressed. The only other abnormality was a haemangioma of the lower lip. A laryngoscopy was performed under a general anaesthetic. The larynx was red and some subglottic swelling was seen which was thought might be due to infective oedema. Following this examination the stridor was very marked but was relieved by nursing in an atmosphere saturated with water vapour. A respiratory infection delayed further investigation for two months when a further laryngoscopy showed a symmetrical subglottic swelling which appeared to be either inflammatory oedema or a haemangioma. The stridor and respiratory obstruction which followed this examination necessitated a tracheostomy.

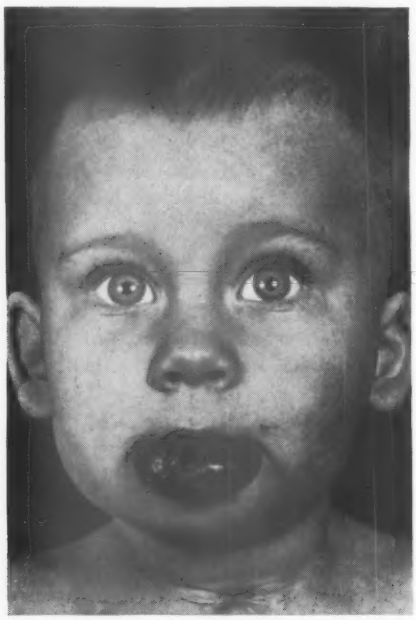

FIG. 1.—Case 1. Child after removal of tracheostomy tube.

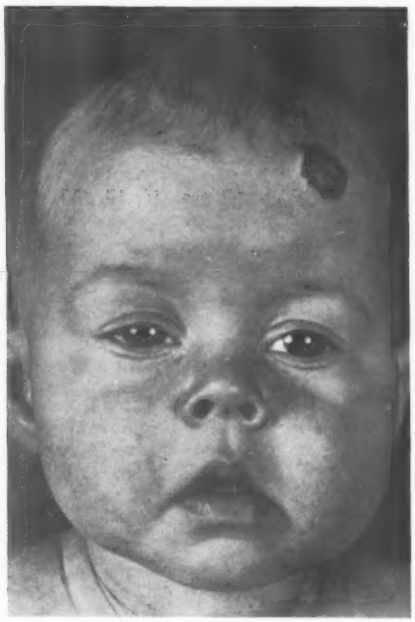

FIG. 2.—Case 2.

Because of the haemangioma on the lip it was assumed that the swelling seen was haemangiomatous and the

subglottic region was irradiated by means of deep x-ray (250 R.). The treatment was followed by considerable tracheal obstruction and respiratory distress. A month later laryngoscopy showed that the subglottic swelling was larger, and a biopsy confirmed the diagnosis of haemangioma. A second course of irradiation (200 R.) caused no reaction and one month later an attempt was made to remove the tracheostomy tube under sedation. The child tolerated laryngeal respiration for two days until increasing dyspnoea and stridor compelled the replacement of the tube. Bronchospasm and respiratory infection followed and congestive cardiac failure developed. This was controlled with digoxin and antibiotics and a third course of deep x-ray was then given. The treatment provoked no reaction but the tube was left in place because of a pyrexia due to teething and it was finally removed under sedation seven months after admission. Progress was satisfactory and a later laryngoscopy showed a good airway with only some residual swelling in the subglottic region. The child was discharged home eight months after admission. She has attended for treatment to her lip but has had no more stridor.

Case 2. (Fig. 2.) J.G., also a girl and a second child, was born on February 5, 1957. A laryngeal stridor was first noticed at 6 weeks of age and gradually became worse finally becoming very marked with a cold. There was some feeding difficulty. When seen at another hospital a lateral radiograph of the soft tissues of the neck showed a rounded swelling partly blocking the trachea below the cords. She was transferred to The Hospital for Sick Children and was found to have a biphasic stridor with rib recession. There was, in addition, a small haemangioma of the forehead which, the mother said, had gradually enlarged since birth. Laryngoscopy revealed a rounded swelling arising from the posterior wall of the subglottic region. A biopsy taken from this swelling showed that it was a partly canalized haemangioma. Considerable stridor followed this operation but a tracheostomy was avoided by nursing in a humid atmosphere for 24 hours. The subglottic region was irradiated twice with an interval of two weeks by means of deep x-ray (250 R. and 200 R.). No reactions followed and two days after the second treatment the stridor ceased. A month after admission she was discharged home and has had no subsequent trouble.

Comment

Haemangiomata are malformations rather than neoplasms and canalization accounts for their seeming growth (Willis, 1948). This gradual enlargement was observed in the first case recorded here. The condition is probably not as rare as the few records suggest and reports of a number of cases have appeared recently (Baker and Pennington, 1956). The records are all very similar. Though it has been suggested that this condition occurs more often in males there is no difference in the incidence between the sexes in the small number recorded. Stridor usually becomes apparent during the first three months of life as canalization occurs. It is the presenting symptom. The site of the haemangioma is usually the subglottic region or the upper trachea, though the supraglottic region has been affected and in one case (Baker and Pennington, 1956) the mediastinum and bronchi were involved. In over half the number there were other haemangiomata, usually on the head and neck. The mortality is considerable and nine of the 21 cases have died of respiratory obstruction.

The most satisfactory treatment has, in all cases, proved to be radiotherapy (Suehs and Herbut, 1940; Ferguson, 1944; Kasabach and Donlan, 1945; Crooks, 1954) and though there is some theoretical danger to the developing larynx there are no reports of such damage. The second case described here is the only one recorded where a proven haemangioma has been successfully treated without tracheostomy. The two case histories are an interesting comparison in this respect as the first shows that the hazards of a tracheostomy and the difficulty in removing the tube markedly increase the risk to the child and the time spent in hospital. In many cases, of course, tracheostomy must be performed on admission and an increase in the size of the haemangioma following irradiation may lead to sudden respiratory obstruction. However, provided that everything is in readiness for an emergency operation, the risk of irradiation without an elective tracheostomy appears to be justified.

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INTRASPINAL NEUROBLASTOMA IN A NEWBORN BABY

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 4, 1957)

Intraspinal and spinal cord tumours are quite rare in childhood. Most authors reporting cases of tumours found within the spinal canal use the term 'spinal cord tumour' in a broad sense without regard to whether they are spinal cord tumours proper or of extradural origin. In this paper we refer to an 'intraspinal' neuroblastoma in a newborn infant, and wish to emphasize that though it is intraspinal, yet it is not a tumour of the spinal cord proper, but is situated extradurally.

Anderson (1953) described 21 cases, of which the youngest was 5 months old. Dandy (1925) reported on such tumours in 36 patients of whom five were under 15 years of age. Ford (1944), amongst 70,000 neurological cases in children, found only three spinal cord tumours, the youngest child with this type of tumour being 9 years old. Stookey (1928) analysed 160 cases of spinal cord tumour of which only eight were under 12 years of age. In Elsberg's series (Elsberg, 1925) the youngest patient was 3 years old and Buchanan's youngest patient was aged 3 months (Buchanan, 1950). In the entire world literature, according to Mosberg (1951) and Elefant, Jeklerová and Lesný (1955), altogether 25 cases diagnosed during the first year of life have so far been described. Mosberg's studies have also shown that 75% of all spinal tumours diagnosed during the first year of life consist of lipomas, dermoids, teratoids or teratomas.

Ingraham and Matson (1954) divide intraspinal tumours in children into three groups: (1) congenital tumours, ranging from simple dermoid cysts to highly variable tridermal teratomasi; (2) intramedullary gliomas, including astrocytomas, ependymomas, medulloblastomas and multiform glioblastomas ; (3) extradural extension of paraspinal lesions, including neuroblastoma, reticulum cell sarcoma and lymphosarcoma.

Omitting cases of teratoma, dermoid and tumours associated with developmental anomalies such as spina bifida, meningocoele or sinus pilonides, the present authors were unable to find in accessible literature more than two cases of pure spinal cord tumour diagnosed in the newborn (Katcher, 1952; Parkinson, Medovy and Mitchell, 1954). They therefore consider it appropriate to record the following case.

Case Report

M.L. is the second son of a mother who during the second month of her pregnancy suffered from renal colic and from the eighth month with sciatica-like pains. Normal delivery took place at a maternity hospital on June 23, 1955, of a lively baby weighing 3·580 Kg. and measuring 52 cm. in length. On the 5th day the hospital paediatrician (Dr. R. Nosková) discovered considerable flabbiness of the lower limbs, especially the left, and laxity of the joints. On the following day the condition was worse: the legs were cool, the tonus was lowered, more so on the left side where no reflexes could be elicited. The baby was transferred on the same day to the Third Paediatric Clinic for investigation.

On admission the lower limbs were cool and the soles of the feet cyanotic; Moro's reflex showed no brisk response in the lower limbs. Spontaneous movement of the right leg was weak, and dorsiflexion of the left foot absent; the calf muscles were hypotonic on both sides, more so on the left, and possibly even hypotrophic. The anus was gaping and the perineum around it formed a pouch-like bulge, thought to be due to paresis of the pelvic floor muscles, which when compressed produced a stream of urine. A barium enema and cystoradiography revealed no abnormality. Lumbar puncture on the 15th day produced only a small amount of xanthochromic cerebrospinal fluid with a light admixture of blood. Plain radiographs of the spine showed sinistroscoliosis with maximal curving of the upper lumbar portion. At this level there was also a suspected dilatation of the spinal canal which was particularly apparent in a lateral view. The arches of the 1st and 2nd lumbar vetrebrae were conspicuously thin, and formed an angular kyphosis (Figs. 1 and 2). On the basis of these findings an expansive process within the upper lumbar portion of the spinal canal was suspected (neuroradiologist, J. Jirout).

On July 13, when the infant was 3 weeks old, pneumoperimyelography was carried out (Figs. 3 and 4). Following insufflation of 20 ml. of air by the lumbar route in a

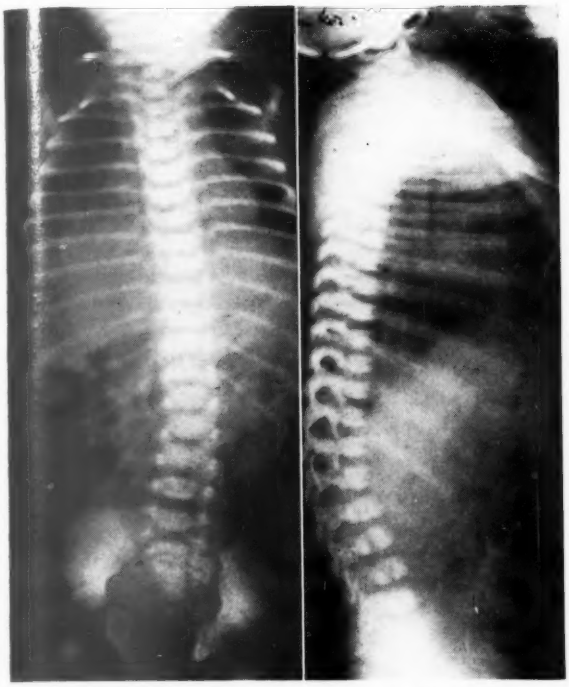

FIG. 1.

FIG. 2.

FIG. 1.—Plain radiograph of spine (anteroposterior).

FIG. 2.—Plain radiograph of spine (lateral).

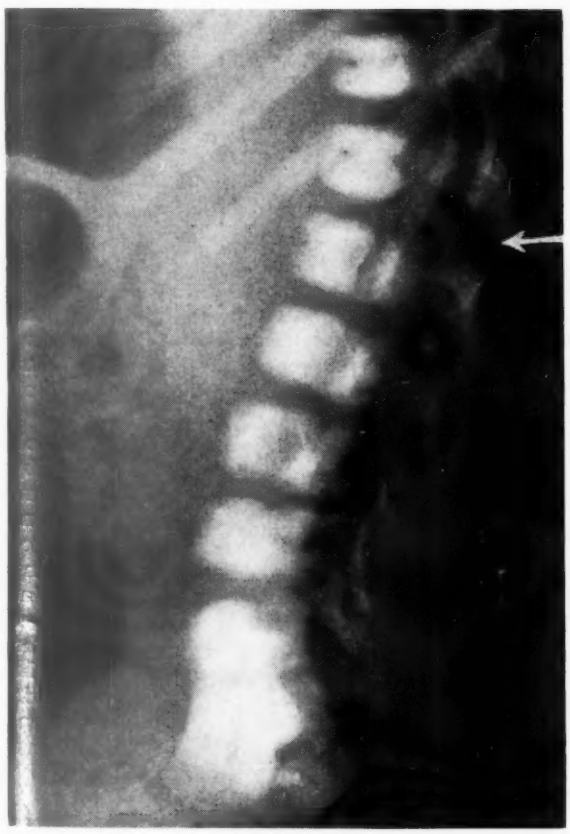

FIG. 3.

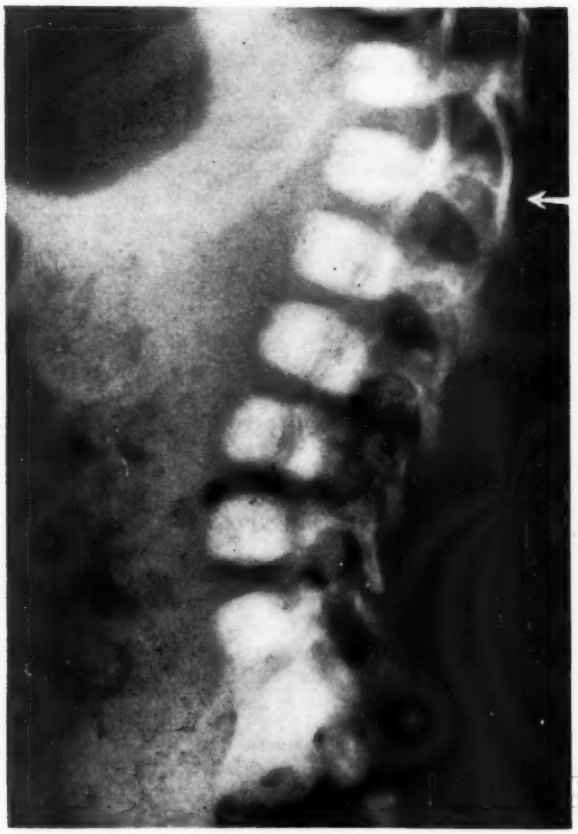

FIG. 4.

FIG. 3.—Pneumoperimyelogram. The air filling extends up to arch of L1 (marked by arrow).

FIG. 4.—Pneumoperimyelogram. On slightly raising pelvis the air filling reaches upper border of arch of L1 (marked by arrow).

lying-down position, the lateral view radiographs revealed an air filling in the sacral and lumbar portions extending cranially up to L2. This is in keeping with pressure changes above L1 (J. Jirout).

At the same time a sample of cerebrospinal fluid was withdrawn and examined: the fluid was blood-stained and, after centrifuging, mildly xanthochromic, with 103 lymphocytes and numerous erythrocytes. Pandy's reaction was ++++, Ross Jones +++, Nonne Appelt +++, and the protein 0·86 g. per 100 ml. A radiograph of the lungs showed a light shadow over the right cardiophrenic angle. The baby was afebrile throughout.

At a neurological examination on July 15 it was found that since the previous examination the movement of the left leg as well as the tone of the calf muscles of both sides had improved. Spontaneous mobility of both lower limbs was symmetrical, though in suspension the right lower limb was more feeble. The reflexes of L5-S2 were absent on both sides. The perineal bulging continued on both sides while the anus was somewhat more gaping than a week earlier. It was decided that the findings were consistent with compression of the cauda.

Improvement in the mobility of the lower limbs was observed after the first lumbar puncture. Since, during a second lumbar puncture, a quantity of dark blood had escaped, a haemangioma was believed to be present, which diminished in size after puncture and so exerted less pressure on the cauda equina. Laminectomy of L1-L2 was recommended.

The baby was operated on at the age of 28 days on July 22, 1955, at the neurosurgical department of the Střešovice Hospital in Prague, and laminectomy of L1-L2 was performed under local anaesthesia. Beneath the arches a bluish violet tissue with a delicate capsule was found, which at first gave the impression that a haematoma beneath the dura mater was present. On closer examination, however, it was found to be neoplastic tissue which it was possible to remove gradually with comparatively little haemorrhage. It had grown practically across the entire antero-posterior dimension of the spinal canal. Not until the greater part of the tumour had been removed could it be established that the pouch of the dura mater was pressed forward and to the left, whereas the remainder of the canal was filled by a tumour which extended even under the arch of T12. The latter arch was also removed but the tumour reached even higher. In the lower part of the tumour there was a cyst the size of a pea filled with a greyish yellow caseous substance. The upper part of the tumour was penetrated through and through by one of the nerve roots, as was confirmed by the response to traction. In view of the extent of the laminectomy and the fact that the baby began to breathe more quickly and the pulse rate to rise, it was decided to discontinue the operation even though the entire tumour had not been removed.

Histological examination of the excised mass was carried out by M. Vorreith who found portions of strongly haemorrhagic tumorous tissue and nerve ganglion. The tumour cells were comparatively small, mostly rounded in shape with a dark nucleus and a well-defined basophilic cytoplasm. In some parts between the islets of cells there was a fibrillary structure, pointing to the neurogenic nature of the tumour. In numerous places the tumour cells constituted rosette-shaped formations. In the portions broken up by haemorrhagic areas there were occasional leucocytic infiltrations and foci of siderophages. Mitoses were not found. He concluded that the findings were consistent with neuroblastoma.

Following the operation the baby was in good condition, drank well and gained in weight. From early in July to early August, 1955, the baby was given radiotherapy: 100R were administered in each of 26 sittings by V. Stašek. During this treatment only once was there a change in the blood count, the erythrocytes falling to 3,760,000, the haemoglobin decreasing to 60% and immature white cells making their appearance.

Before discharge the baby was re-examined neurologically. Signs of affection of the cauda were still present, more so on the left side, but compared with the findings before operation there was pronounced improvement on both sides, especially at the right. Before discharge the baby was thriving satisfactorily and at the age of 3½ months weighed 5·31 Kg.

Of the laboratory and other investigations we record the following results: the blood group was A rh; the W.R. negative; an electrocardiogram revealed tachycardia, but was otherwise normal; a radiograph of the lungs on August 5, 1955, showed elevation of the right diaphragm.

The baby was readmitted for six days on January 22, 1956. The ocular fundi were normal. The blood picture showed 4,490,000 erythrocytes, 74% haemoglobin, 8,300 leucocytes; polymorphs with rod-shaped nuclei 4%, with segmented nuclei 36%; lymphocytes 59%; and monocytes 1%.

At 7 months of age the flaccid peripheral paresis of the lower limbs was still present but the sphincter signs were much improved. As against the earlier picture it was now the right lower limb that was the more affected of the two. A radiograph of the skeleton showed no destructive changes, nor evidence of metastases, and there was no scoliosis; only at the sites of the laminectomy the vertebral bodies were more translucent. At home exercises were being carried out with the baby according to instruction.

The third stay in hospital at the age of 11 months took place between May 25 and June 16, 1956. The baby weighed 10·3 Kg. and measured 76 cm. The circumference of the head was 47 cm., and of the chest 49 cm. The baby had sat up without support from the age of 10 months, was standing and could already walk holding on to the cot. Dentition began at 8 months, speech at 10 months. By this time the anterior fontanelle was closed, the occiput firm, and the operation scar in the thoracolumbar region of the back well healed. The blood picture continued to be normal. A radiographic examination of the chest showed elevation of the central portion of the right diaphragm, while one of the skeleton showed no metastases, and normal ossification of the long bones. The ocular fundi were normal.

At the age of 12 months a further neurological examina-

tion showed peripheral hypotonia of the left lower limb. There was a slight pes valgus on the left. When the left lower limbs was moved spontaneously extension of the foot was carried out incoordinately by means of the extensor muscles of the toes; tibialis anterior responded well to stimulation and showed normal tonus. Patellar reflexes were increased on both sides. The plantar reflexes were of the extensor type. The reflexes of L5-S2 were bilaterally decreased. There was a physiological lumbar lordosis. With support the baby stood comparatively firmly, the centre of gravity being transmitted to the right leg. Micturition was streamlike, the flow of urine was promptly halted and did not dribble. away. The anal sphincter was well-contoured though slightly enfeebled; the anal reflex could not be elicited. As far as sensation was concerned, there was a loss of pain sensibility on the right side distally from L4, on the left from L5.

Since the abnormal neurological findings were receding, no further radiotherapy was recommended for the time being. The myelogram showed no tumour cells and the marrow was normal.

The baby began walking without support at 18 months. It was last examined at the age of 20 months, when it weighed 12·75 Kg. It had one regular daily stool and micturition was normal. Its mental development was in keeping with its age. The sensory disturbance in the region of S2-S3 persisted as well as mild hypotonia of the right S1-S2 segments but otherwise the neurological findings had almost returned to normal.

Discussion

It is not intended to deal here with the clinical entity of spinal cord compression as such, which in childhood presents numerous features in common with compression in the adult. It should, however, be recalled that, just as in intracranial tumours, intraspinal expansive processes have their syndrome of hypertension. Apart from changes in the composition of the cerebrospinal fluid (increased protein, xanthochromia), changes in its pressure and disorders in its circulation may help in diagnosis. They are an equally valuable diagnostic help in children even though in the younger ones their evaluation is more difficult because of lack of co-operation. In the younger subjects sensory and root manifestations have a greatly restricted value in determining the levels of localization since here it is a matter of estimating the approximate level of disordered sensation on the basis of the child's general reaction, elicited as painful stimuli passing from a zone of diminished or absent sensitivity, hypoaesthetic or anaesthetic, to a normal or hyperaesthetic one.

On careful examination of plain radiographs of the spine in cases of cord compression, dilatation of the spinal canal, occurring especially in children and confined to a few segments, cannot be missed. Note is taken of the interpedicular distance, flattening of the inner surfaces of the pedicles or their possible disappearance. The changes are greatest at the level of the tumour, below which they decline in magnitude. Another important feature is the change in the normal shape of the spine. At the site of the expansive process the spine is altered in shape over a small area, being straightened as if it were stiff, or there may be a scoliosis confined to a brief segment of the spine (Jirout, 1956). Impressions of the posterior wall of the vertebral body and dilatation of the intervertebral foramina are diagnostically as valuable in childhood as they are in adults. An accurate spatial picture of the boundaries of the expansive process may be obtained with the aid of pneumoperimyelography, which is kinder to the patient than iodine perimyelography.

The authors' own experience as well as that recorded in the literature (Ingraham and Matson, 1954) shows that the most frequent erroneous diagnoses in cases of spinal cord compression are poliomyelitis or amyotonia congenita.

The symptomatology of our present case included a feature which we have not so far come across either in our experience or in the literature. This was paresis of the pelvic floor manifesting itself by a pouch-like bulge, in the differential diagnosis of which a cystic formation within the pelvis had to be excluded.

In view of the clinical signs of compression of the cauda equina and the corresponding changes in the radiographs of the spine, together with the results of pneumoperimyelography, the upper boundaries of the compression were not searched for. Prompt improvement of mobility following operation, even though the entire tumour had not been removed, justifies the belief that it did not extend higher than one segment above that reached at operation. There is reason to believe that early operative intervention on the 28th day of life—the patient being perhaps the youngest ever subjected to such an operation—was responsible for the remarkable disappearance of the clinical signs and the fact that the child is now free from gross motor disability.

The effect of the radiotherapy cannot be unequivocally evaluated in the light of the latest findings on the spontaneous remissions of the malignity in neuroblastoma (Cushing and Wohlbach, 1927; Lehmann, 1932; Farber, 1940). Gross (1953) as well as other workers have found that neuroblastoma treated before the age of 2 years has a more favourable prognosis than those diagnosed later.

Neuroblastoma, one of the most frequent malignant tumours in childhood, originates primarily in paraganglionic areas but often penetrates into the

spinal canal via the intervertebral foramina. It is a highly vascular, fairly soft, cellular tumour; it never, however, penetrates the dura mater or nerve sheaths. Its aetiology and pathogenesis are not clearly understood. If signs of rapid progression of the cord compression are present it would be wrong to await the effect of irradiation or other conservative treatment. In such cases laminectomy with complete excision of the intraspinal tumour is called for as soon as possible. Such treatment with subsequent radiotherapy leads to functional restoration. Extensive laminectomies in small children may lead to spinal deformities (lordosis, kyphoscoliosis). By combining surgical measures with radiotherapy, Wittenborg (1950) found that 30% of patients with neuroblastoma survived over three years. In general, however, and with rare exceptions—a survival of 15 years (Lehman, 1932) and one of 17 years (Oberkircher, 1953)—the disease ends fatally within one year. It is noteworthy that Lehman's case was not treated radiologically at all.

Summary

The literature is surveyed on spinal cord compression in children in general and in infants and the newborn in particular.

A case of intraspinal neuroblastoma is described, which was diagnosed in a newborn baby on the eighth day after birth, and treated on the 28th day by laminectomy with partial extirpation of the tumour and post-operative radiotherapy.

A follow-up at the age of 20 months showed very good results from the surgical treatment and possibly also from the post-operative radiotherapy. The child walked safely without support and there were no signs of incontinence or metastases.

The baby was re-examined at the age of 34 months and its neurological condition was found to be unchanged.

To our knowledge it is the third case of pure intraspinal tumour in the newborn recorded in world literature.

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SOME UNUSUAL FINDINGS IN A FAMILY WITH FRIEDREICH'S ATAXIA

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(RECEIVED FOR PUBLICATION NOVEMBER 11, 1957)

Introduction

Friedreich's ataxia, a hereditary disorder of the nervous system, is characterized by the onset of ataxia of gait, weakness and clumsiness of the limbs, and dysarthria of speech in young patients of either sex. Loss of tendon reflexes, usually combined with extensor plantar responses and impairment of vibration and joint sense, is often found. Nystagmus is common. Complications include mental symptoms, kyphoscoliosis, pes cavus and claw hand. Cardiac complications often terminate the disease. These findings are associated with progressive degeneration of the spinocerebellar and cortico-spinal tracts, the posterior column and Clarke's column.

A family, in which a father and six of his children are believed to suffer from Friedreich's ataxia, is reported because of several unusual features. Notably, optic atrophy and nerve deafness are the most consistent findings, and upper and lower motor neurone disturbances appear more conspicuous than those of the spino-cerebellar system. The rate of progress of the disease varied considerably : one child died within two and a half months of the onset of symptoms, whilst others with muscle wasting appeared to remit during the period of observation.

Before the diagnosis was finally established in the members of this family many conditions were considered. These included tuberculous meningitis, Arnold-Chiari malformation, posterior fossa lesion, spinal tumour, progressive muscular atrophy, peripheral neuritis due to avitaminosis, diphtheria, lead poisoning, toxic myelitis, and syphilis of the nervous system and meninges.

Family History

The medical history of the family preceded the period of observation, 1955-1956, by at least 16 years. The family consisted of the parents and nine children, four of whom died, three of these had nervous symptoms and signs. Both parents were Gentiles and were unrelated. The mother, 45 years, was quite well with no muscular weakness or ataxia. She had a long standing internal strabismus of the left eye but there was neither optic atrophy nor nystagmus. She was not deaf. The father, 44 years, suffered from childhood poliomyelitis which resulted in shortening of one leg. He had severe impairment of hearing, poor vision, bilateral optic atrophy and normal hands. His gait though cumbersome, due to his shortened leg, did not appear ataxic and he walked well unaided. His visual and auditory symptoms were slowly progressive for a number of years. Enquiry into the family tree revealed no history of disease of the nervous system in other members (Fig. 1).

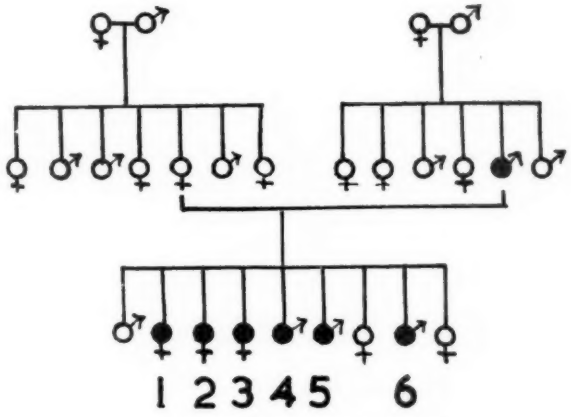

FIG. 1.—The family tree, with case numbers.
● = affected person.

The first child, a boy, not affected with nervous symptoms, was born in 1935 with bilateral talipes. He died of pneumonia at 3½ years. Necropsy revealed a well-nourished child with a large thyroid. Examination of the nervous system was not done.

Three girls and two boys who developed symptoms and signs of nervous disease were born in 1937 (Case 1), 1939 (Case 2), 1942 (Case 3), 1944 (Case 4) and 1946

(Case 5). A daughter, born in 1948, was alive and well, but a son born in 1949 (Case 6) had nervous symptoms and signs. The youngest child, a daughter born in 1951, was unaffected and well.

Three children died (Cases 1, 2 and 5) and necropsies were done on two patients but, unfortunately, war damage destroyed reports and specimens. However, some specimens of Case 1 were obtained from the Pathology Department of Liverpool University and these are available for study. They include cross sections of the mid-brain, pons, medulla, cervical, thoracic and lumbo-sacral cord, and the optic nerve, which have been stained with haematoxylin and eosin, Loyez's and Marchi's methods.

Special investigations were carried out on some of the five patients. The results were as follows: (1) The Wassermann reaction was negative (Cases 2, 3, 4, 5, 6) and in both parents. (2) Toxoplasmosis dye and complement fixation tests (Cases 3, 4, 6) and in the mother were negative. (3) Radiographs of skull and spine (Cases 1, 2, 3, 4, 5) were normal with the exception of Case 3 which showed a slight degree of platybasia. (4) Electrocardiography, normal results (Cases 3, 4, 6). (5) Urinary lead, copper, amino acids and phenylpyruvic acid estimations were within normal limits (Cases 3, 4, 6). (6) Vitamin A absorption was within normal limits (Cases 3, 4, 6). (7) Plasma electrophoresis was normal (Cases 3, 4, 6). (8) Electromyography was normal (Case 6). (9) Muscle biopsy (Case 4) revealed normal muscle. (10) Cerebrospinal fluid appeared normal (Cases 1, 2, 3, 4, 6). If any comment could be made, it was that the sugar content showed a constant tendency towards the low side of normal (between 50 and 60 mg. /100 ml.). (11) The fasting blood pyruvic acid was determined in Cases 3, 4 and 6 after the method of Friedemann and Haugen (1943). The value was within normal limits (0·5 to 1·1 mg./100 ml.) in Cases 3 and 4 but raised (1·7 mg./100 ml.) in Case 6. An hour after a loading dose of glucose the levels remained within normal limits (1·7 to 2·3 mg./100 ml.) in Cases 3 and 4, but in Case 6 a raised value persisted (3·1 mg./100 ml.). The reason for this was not clear.

All the affected children were born normally and were healthy infants. Milestones (holding up the head, sitting, standing and walking) were passed normally. Up to the onset of symptoms all had been healthy with the exception of Case 2, who had a sacrococcygeal pelvic tumour removed surgically at 9 months, and Case 6, who had a congenital strabismus at 3 years which had been satisfactorily corrected by the time symptoms developed. Cases 3, 4 and 6 suffered minor head injuries but these were not severe enough to cause concussion.

Impairment of vision and hearing were the most constant symptoms in children and father; slow to start, they were gradually progressive. There was no history of middle-ear disease. A similar picture was seen in the optic fundi of the father and Cases 2, 3, 4, 5, and 6. The discs, uniformly pale, stood out distinctly from an apparently normal retina. In Case 2 the left disc was involved but in the others both discs were affected. In Case 1 the fundi were thought to be healthy during life but after death demyelination of the optic nerve was found. Fields of vision (Cases 3, 4) showed peripheral constriction with no central scotoma. Light reflexes, where noted, were present (Cases 2, 4, 5, 6). Tests for the auditory nerve (Rinne and Weber) revealed impairment of bone and air conduction. The tympanic membranes appeared healthy. On this evidence it was assumed that deafness was nervous in origin. The degree of deafness varied; it was slight in Cases 1, 2, and 6, moderate in Case 4 and severe in Cases 3 and 5, causing Case 3 to attend a school for the deaf, where her poor visual acuity restricted her ability to learn lip reading. All the patients learnt to speak, if somewhat monotonously and monosyllabically, and were not considered to be grossly dysarthric.

Four children had nystagmus (Cases 1, 2, 4, 5). In Case 1 it occurred in all directions, it was horizontal in Cases 2 and 4, and rotatory in Case 5. The facies were expressionless and on smiling the lips were transverse. Other cranial nerves appeared intact, with no other signs of bulbar involvement.

None of the patients had convulsions or tremors. Mentally, they were dull and were either irritable (Cases 1, 5) or apathetic (Cases 2, 6). Acute fright and attacks of clinging to the mother overcame Case 5 periodically.

To add to the misery of this family, the parents often quarrelled about their responsibility for the children's plight. In particular, the father blamed the mother, because of the 'turn in her eye', which he considered to be the cause of the children's eye trouble, and as a result he often sought the companionship of other women thereby creating a further difficulty.

Other physical findings are listed in Table 1.

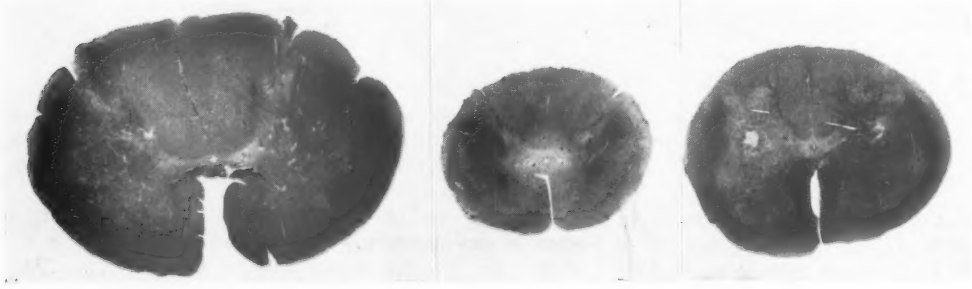

FIG. 2.—Demyelination of posterior columns, dorsal and ventral spino-cerebellar tracts in sections of cord at cervical, thoracic, and sacral levels. Loyez ×5.

TABLE 1

PHYSICAL FINDINGS IN FAMILY WITH FRIEDREICH'S ATAXIA

Case No.	1	2	3	4	5	6
	Female	Female	Female	Male	Male	Male
Age of onset (in years) ..	2½	7¾	9	9	5 1/6	5 1/6
Symptoms:						
presenting	Fatigue	Impaired hearing	Impaired hearing	Failing vision	Difficulty in fastening buttons, turning doorknobs	Leaning on things for support
subsidiary	Weakness and leaning on things for support. Rolling of eyes. Unsteadiness of hands when holding objects	Weakness of hands. 'Pins and needles' in hands, feet. Unsteadiness in walking, with stiff legs, high steppage	Unsteady gait. Poor vision. Headaches	Deterioration in hearing	Deafness. Irritability. Muscle weakness. Difficulty in walking: often toppled forward. Failing vision	Difficulty in fastening belt clasp
duration	Died within 2½ mth. from 'demyelinating myelitis'	Died 19 mth. later from 'toxic polyneuritis'	4 yr.	1 yr.	Died 3½ yr. later from pneumonia	8 mth.
Past history	Healthy	Sacrococcygeal tumour removed at 9 mth.	Minor head injury	Minor head injury	Healthy	Minor head injury. Congenital strabismus at 3 yr.
Motor Function:						
Posture	Dorsal kyphosis	Normal	Lordosis	Scoliosis. Pes cavus	Claw hand	Slumped forward in sitting position
Tone	Poor in arms	Increased in legs	Normal	Normal	Increased in legs	Poor all limbs
Power	Weakness both arms	Weakness of grip	Good	Good	Weakness arms and legs	General weakness
Wasting	None	Marked in small muscles, hands, deltoids	None	Deltoids and spinati, hands	Deltoids with scapular and thenar muscles	Supra and infra-spinati
Fibrillation	Not noted	None	Deltoids	Quadriceps	None	Spinati
Sensory Function:						
Tactile sensitivity ..	Not tested	Normal	Normal	Normal	Not tested	Not tested
Pain sensitivity	,,	,,	,,	,,	,,	Normal
Joint position	,,	Not tested	,,	,,	,,	,,
Vibration sense ..	,,	Normal	Absent in ankles	Absent in ankles	,,	,,
Reflexes:						
Plantar	Extensor	Bilateral extensor	Normal	Normal	Left extensor	Normal
Abdominal	Absent	Present	Present	Present	Present	Present
Deep	Not tested	Increased especially in legs with knee clonus	Absent ankle jerks	Diminished	Diminished but increased left leg	Normal
Coordination:						
Finger to nose test ..	Not tested	Normal	Normal	Intention tremor right hand	Not tested	Normal
Heel to knee	,,	Not tested	,,	Normal	,,	,,
Rombergism	,,	Positive	Positive	Positive	,,	Negative

Histology

Examination of the sections from Case 1 showed that degenerative changes were most marked in the cord (Fig. 2) where symmetrical demyelination involved the tracts of Goll and Burdach, the anterior and posterior spino-cerebellar tracts and the cortico-spinal tracts. Demyelination could be discerned in the area of Monakow and lateral aspect of the restiform body in the medulla, but the pyramids and the medial lemnisci appeared intact. The normal orderly arrangement of

the axons was replaced by many irregular distended spaces. Towards the periphery of the involved tracts the contents of many of these spaces stained with osmic acid. Axis cylinders were difficult to define and it was not possible to say whether they were reduced in number. The anterior and posterior nerve roots stained with osmic acid.

The entire grey matter of the cord was congested, there was no oedema or perivascular cuffing. Two haemorrhagic cystic spaces had formed in the postero-lateral regions of the grey matter in the sacral cord. The walls of the vessels in the cord and meninges appeared normal and so did the meninges.

There was widespread damage of nerve cells. Some stained densely, the nucleus being eccentric and the chromatin network lost. Others appeared swollen and contained a feebly stained and eccentric nucleus, the chromatin being either arranged around the periphery of the cell or completely absent. Satellitosis was observed around some of the swollen cells.

Areas showing nerve cell damage included the grey matter of the cord (in one thoracic section they were completely absent), the cuneate nucleus, the Vth nerve nucleus, and the substantia nigra. Both anterior and posterior horns of the cord were affected as well as Clarke's column. Glial cells appeared increased in both grey and white matter.

Concentric demyelination was seen in the optic nerve.

Two sections of the cord and one of the optic nerve were stained by Holzer's method. By this means an increase of glial tissue was demonstrated in the posterior columns, the posterior spino-cerebellar tracts, the anterior horns, Clarke's column and in the optic nerve.

No abnormality could be detected in the vestibular nuclei and the trapezoid bodies. The auditory pathway could not be studied in the limited number of sections available. The superior and medial accessory olivery nuclei, the pontine nuclei, the Xth and XIIth nerve nuclei appeared normal.

Discussion

Diagnosis. Even when it became clear that the disorder was heredo-familial, its nature remained uncertain because the clinical picture varied so much. Bogaert (1948) observes that the more complex a heredo-degenerative disease seems anatomically, the more it appears to merge with other groups. For this reason familial amyotrophic lateral sclerosis was diagnosed in Cases 3, 4, 5 and 6 because signs of upper and lower motor neurone disease were prominent. However, posterior column loss (Cases 3, 4), nystagmus (Cases 4, 5) and intention tremor (Case 5) cast doubt upon this diagnosis.

Greenfield (1954) discusses the association of Charcot-Marie-Tooth and Roussy-Levy syndromes with Friedreich's ataxia because their pathological features are similar in some respects. The points of clinical similarity with these syndromes in the present family are 'main-en-griffe' (Case 5), reduction of the deep reflexes (Cases 3, 4, 5), spinal deformities (Cases 1, 3, 4), remissions (Case 6) and degeneration in dorsal columns, pyramidal and spino-cerebellar tracts and loss of cells in Clarke's column. Points of difference are the presence of nystagmus, intention tremor and absence of characteristic wasting of the peroneal and anterior tibial muscles.

Friedreich's ataxia was considered the most likely diagnosis in the light of all the symptoms and signs of the patients and the histopathology of Case 1

Optic Atrophy and Nerve Deafness. Optic atrophy is not uncommon in Friedreich's ataxia; Sjögren (1943) found an incidence of 12%. The form varies, as in other hereditary ataxias. A retinal type, in which there is degeneration of the retina and choroid with an increase in pigmentation was described by Franceschetti and Klein (1948), and designated 'tapeto-retinal degeneration'. Neuritis of the optic nerve head and retrobulbar neuritis may also be seen. André-van-Leeuwen (1948) suggested three varieties of this form.

The first shows typical retrobulbar neuritis in which vision is rapidly diminished, sometimes considerably, there is a central scotoma and temporal pallor of the disc. Peripheral fields are usually little affected. Sometimes lesions extend beyond the papillo-macular bundle when there is deficiency in the peripheral fields of vision. The age of onset is 30 to 40 years.

The second shows rapid onset of optic nerve degeneration with considerable loss of vision almost to the point of complete blindness. The disc is pale and there is considerable shrinkage of the visual fields. In less advanced cases central as well as peripheral vision may be lost. This type usually comes on about puberty although it may appear congenitally or in early infancy.

The third shows loss of vision of less sudden onset with peripheral constriction of the visual fields which is seen more typically in the spino-pontocerebellar degenerations. Pallor of the discs may be complete or confined to the temporal halves. Sometimes, a discordance between loss of central and peripheral vision may be noticed. Even when a central scotoma is present it may be uncertain whether it is due to retrobulbar neuritis. At other times the picture is that of a slowly progressing optic atrophy. The age of onset is variable and the course slow. The findings in the present family resembled this third type.

Atrophic changes in the papillo-macular bundle of the optic nerve, chiasma and tracts was described by Bogaert in an 11-year-old child with Leber's disease, who died of cerebral haemorrhage and whose cord showed lesions of similar type to those found in Friedreich's ataxia.

André-van-Leeuwen comments that, exceptionally, optic atrophy may precede other nervous symptoms. Sometimes it appears simultaneously, but mostly it follows other symptoms, often by a number of years.

Nerve deafness is much rarer than optic atrophy and their combination is unusual. Bogaert (1948) describes three brothers who suffered from Friedreich's ataxia, two of whom had central deafness and optic atrophy, in whom he regards inheritance as recessive. Unfortunately, necropsies were not carried out, but, in another type of hereditary ataxia, Nyssen and Bogaert (1934) described lesions in a brother and sister in whom there was demyelination of the optic chiasma and degeneration of the primary and secondary pathways of the cochlear system. Degenerated fibres were traced through the restiform body, cochlear nucleus, superior olivery nucleus, trapezoid body, Monakow's bundle and the medial lemniscus to the corpora quadrigemina and internal geniculate body. The cord was not examined. The limited number of sections in the present family made it impossible to compare accurately the histological findings; there was no degeneration of the trapezoid bodies, the medial lemnisci or superior olivery nuclei, but demyelination was present in Monakow's area and the restiform body. Urich, Norman and Lloyd (1957) in studying the auditory pathway of a 10½-year-old girl, who suffered from Friedreich's ataxia, found widespread loss of cells in the central cochlear nucleus. Deafness was not detected clinically but audiometric studies were not done.

Matthews (1950) reported deaf-mutism in three siblings with symptoms and signs of Friedreich's ataxia. A fourth sibling with similar peripheral signs was not a deaf mute.

Clinical evidence of involvement of the vestibular branch of the VIIIth nerve (loss of caloric reaction) was found by Guillain, Mollaret and Aubrey (1935) in 18 cases of Friedreich's ataxia. They found nerve deafness to be rare. They claim that vestibular investigation in Friedreich's ataxia may have some diagnostic value.

Montandon (1948) discusses the auditory, anatomical and pathological implications in hereditary ataxias, and concludes that most lesions causing deafness commence in the labyrinth and may be so slight as to escape detection unless sought carefully by audiometry. The degenerative process tends to spread centrally and when this occurs central deafness masks labyrinthine deafness.

General Comments. Pathogenesis is discussed in most textbooks of neurology and by Greenfield (1954) and will not be repeated here.

The genetic basis of Friedreich's ataxia is beyond doubt. It may be transmitted by dominant or recessive genes. In the present family it is dominant. Some idea of the frequency with which each type occurs is given by Bell (1948) who analysed the findings in 500 pairs of siblings thought to be recessive in origin and 144 pairs thought to be dominant. From the analysis it was found that the age of onset in both groups was similar and that there was a marked tendency for siblings of one family to present symptoms at the same period of life. This last fact may have practical prognostic implications for unaffected and much older siblings, but in the present family in which there are two young unaffected siblings, conclusions on this point cannot yet be drawn.

Matthews suggested that when deaf mutism occurs it may be due to the chance association of two genes. It seems more likely that all the clinical and pathological findings are due to the same process and are attributable to the same causal factor. Diverse anatomical changes in the nervous system, similar to those found in Friedreich's ataxia, have been caused in animals by vitamin A deficiency (Mellanby, 1934) and it seems reasonable to deduce that one gene acting in some similar manner might be responsible for all findings.

Summary

The clinical findings in a family, consisting of a father and six of his children believed to suffer from Friedreich's ataxia, are presented. An unusual feature is the presence of optic atrophy and nerve deafness.

Histological findings in the cord, medulla and midbrain are described.

My thanks are due to Professor N. B. Capon and Dr. R. W. Brookfield for access to their case records at the Royal Liverpool Children's Hospital, and to Dr. J. S. Elwood who helped me with the histology. My colleagues at the Fountain Hospital were kind enough to offer helpful criticism.

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A CASE OF INTRACRANIAL DERMOID CYST ASSOCIATED WITH THE KLIPPEL-FEIL DEFORMITY AND RECURRENT MENINGITIS

BY

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(RECEIVED FOR PUBLICATION OCTOBER 1, 1957)

Intracranial dermoid cysts are rare: of 2,023 verified intracranial tumours recorded by Cushing (1932) there were 15 examples, including epidermoid cysts. In many cases there is an associated congenital dermal sinus. The following is presented as a typical case.

Case Report

D.H. is the second child of healthy parents, the elder child being normal. He was first referred to the Children's Hospital in July, 1954, at the age of 4 weeks because of diarrhoea and vomiting. This was thought to be dietetic in origin, and the only abnormal finding was the presence of the Klippel-Feil deformity, which was confirmed by radiological examination (Fig. 1).

Ten months later he was admitted with acute bronchitis, and examination at that time revealed a small mobile lump in the occipital region. This was considered to be a fibroma.

He then remained well for 15 months until August, 1956, when he was readmitted with a two-day history of refusal to eat, vomiting and drowsiness. He was extremely irritable and crying more than usual, especially if disturbed.

On examination owing to his spinal deformity it was not possible to confirm any neck stiffness. There was no papilloedema.

Lumbar puncture yielded a cloudy fluid containing 3,250 white cells per c.mm., most of which were polymorphonuclear. The protein content was 700 mg. %, the sugar 6 mg. % and the fluid was sterile on culture.

A diagnosis of probable meningococcal meningitis was made: he was treated with penicillin and sulphadimidine and his progress was satisfactory.

Soon after returning home vomiting recurred. He was crying continuously, banging his head and he was noticed to have photophobia. Two weeks later he was readmitted and on this occasion his cerebrospinal fluid contained 1,350 cells per c.mm., of which 75% were polymorphonuclear. The protein content was 60 mg. %, sugar 27 mg. %, and again the culture was sterile. No cause for the relapse of his meningitis was found and he was treated with a course of chloromycetin, and later given a course of tetracycline. Serial lumbar punctures showed a progressive improvement in his cerebrospinal fluid, and coincidently his general condition improved.

Following discharge he remained well for a further seven months, when he was readmitted with a history of vomiting and crying for five days; on examination he had an upper respiratory tract infection, and the cerebrospinal fluid was found to be normal. He was discharged home but within a few days started vomiting. He again had photophobia, his mother thought he had been having

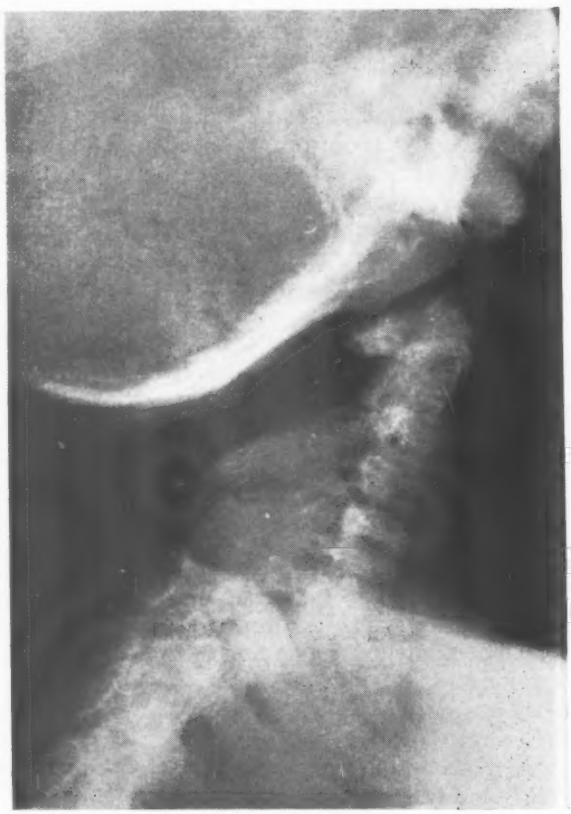

FIG. 1.—Lateral radiograph showing deformity of cervical spines.

he daches, and the history suggested that he probably ha a convulsion on the night before his readmission two we ks later. On examination he was found to have gross bil teral papilloedema. There was now a soft circumscr bed swelling just below and to the left of the extended occipital protuberance. Examination of the skin overlying the swelling showed a small pore from which hairs protruded.

A plain radiograph of the skull showed a small bony defect in the occipital bone just to the left of the midline (Fig. 2).

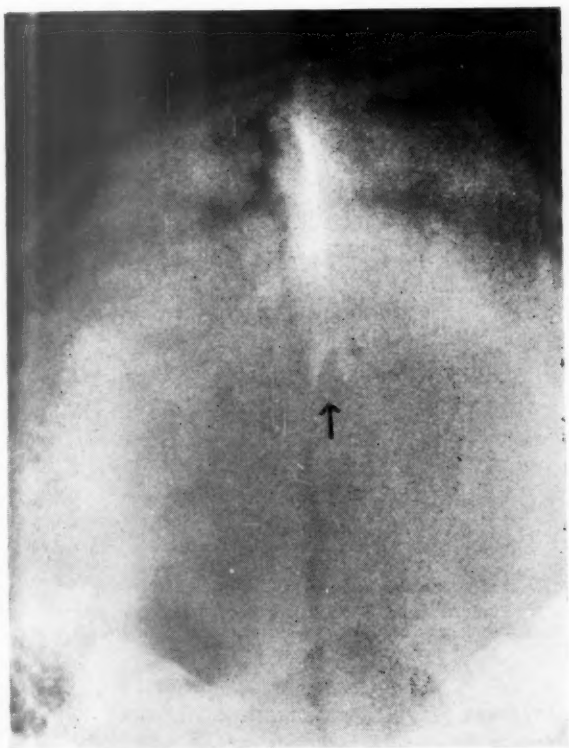

FIG. 2.—Radiograph of skull showing bony defect in occipital bone.

A ventriculogram showed symmetrically dilated but undisplaced lateral ventricles. The third ventricle was dilated and the aqueduct of Sylvius was kinked (Fig. 3). Some air passed through into the fourth ventricle which was not enlarged. The air passed freely down the spine but on returning to the skull most of it accumulated just below the foramen magnum. The findings were considered to be consistent with a mass in the posterior fossa.

The cerebrospinal fluid obtained by ventricular puncture contained 2 cells per c.mm. and less than 10 mg. % of protein.

A pre-operative diagnosis of a dermoid cyst of the scalp associated with a congenital dermal sinus leading to an intracranial dermoid cyst was made, and a craniotomy performed on May 3. The scalp dermoid was excised and a sinus tract was found passing through the occipital bone into the posterior fossa just below the torcular. The dura was found to be very adherent at this point. On opening the posterior fossa a large cystic dermoid was found in the midline. Anteriorly the thin wall of the cyst had become adherent directly to the surrounding brain, and as it was not possible to remove the cyst intact the contents were first aspirated. The cyst was lined with a fairly thick wall of typical glistening desquamated epithelium, and in addition contained a hair. The collapsed cyst was then removed.

The fluid aspirated from the cyst contained numerous pus cells and degenerate Gram positive cocci: it was sterile on culture.

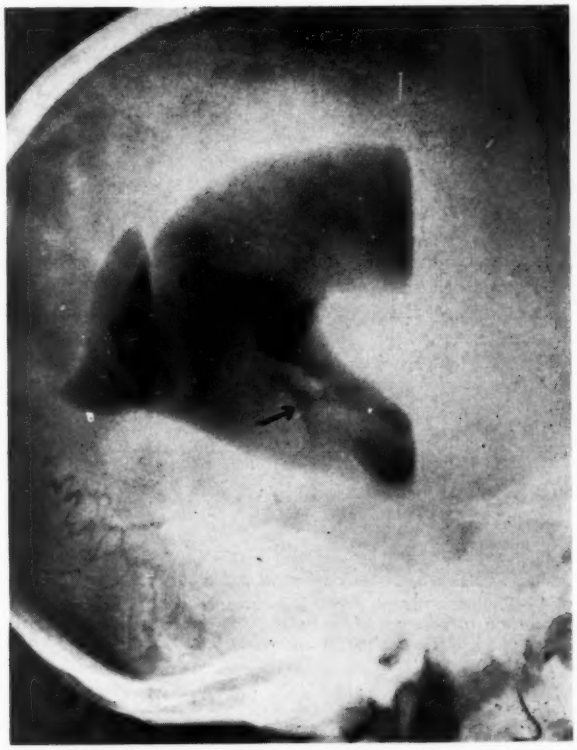

FIG. 3.—Ventriculogram demonstrating kinking of aqueduct of Sylvius by mass in posterior fossa.

Post-operatively he was given a course of tetracyline and his recovery was uneventful.

Pathological Report. The specimen consisted of a stalk of fibrous tissue, 3·75 cm. in length, with a cystic mass at either end. The larger of these cysts was incomplete but appeared to have been approximately 4 cm. in diameter. It had a thin but substantial membranous wall and contained pearly flakes of keratin. A solitary curly hair, 1·4 cm. long, lay within the cyst near its attachment to the cord. The smaller tumour at the other end of the cord was irregular in shape and measured 1·75 cm. in maximum diameter. It had a more fibrous wall, and contained yellowish-brown material and also one or two fine hairs.

A transverse section through the interconnecting cord showed no visible lumen but a firm solid structure of fibrous appearance 2 mm. in diameter.

Histology. The intracranial part of the specimen showed a cavity lined by keratinizing squamous epithelium. A few cerebellar folia attached to it showed patchy degeneration of Purkinje cells but otherwise appeared normal. There was no dural tissue separating the two, but the pia-arachnoid was thickened and infiltrated with lymphocytes and polymorphonuclears (Fig. 4).

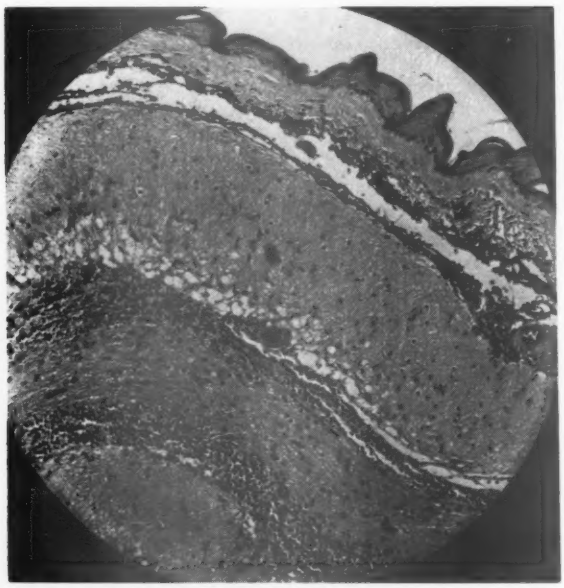

FIG. 4.—Photomicrograph showing intracranial cyst wall and patchy degeneration of adjacent brain tissue. No dural tissue is present. Haematoxylin and eosin × 50.

A section through the stalk showed a solitary remnant of a piece of hair embedded in a core of fibrous tissue (Fig. 5).

The extracranial mass consisted of granulation tissue heavily infiltrated with acute and chronic inflammatory cells. It contained many fragments of hairs with conspicuous foreign-body giant cells, and also some keratinous debris. The diagnosis was of an intracranial dermoid cyst.

Discussion

During recent years there have been several papers reporting cases of congenital dermal sinus but the majority of these have been situated in the spinal axis (Cardell and Laurance, 1951; Perloff, 1954; Haworth and Zachary, 1955; Amador, Hankinson and Bigler, 1955).

Mount (1949) first described two cases of intracranial dermoid cyst associated with congenital dermal sinus. In both cases the cyst was infected forming an intracranial abscess.

Matson and Ingraham (1951) described 10 cases in which there were intracranial complications of congenital dermal sinuses. In nine of their cases the intracranial extension of the sinus was in the posterior fossa, and in the other case there was an infected dermoid cyst in the frontal fossa.

Logue and Till (1952) reviewed the literature and found 25 cases of posterior fossa dermoid cysts to which they added a further seven cases. Of these 32 cases, 22 had no dermal sinus or only an incon-

FIG. 5.—Photomicrograph of section through stalk showing a hair embedded in core of fibrous tissue. Haematoxylin and eosin × 42.

plete sinus. Of the remaining 10 cases with a complete sinus there were seven in which the dermoid cyst was intradural and three were extradural.

More recently, Tytus and Pennybacker (1956) in their paper entitled 'Pearly Tumours in relation to the Central Nervous System' have described a further 43 cases of epidermoid and dermoid tumours. In their series there were eight cases in which the tumour was situated in the midline subtentorially, and of these, three were associated with dermoids of the scalp together with dermal sinuses. One of their patients also had multiple fusion defects of the vertebral column.

The site of the congenital dermal sinus opening is usually marked by a skin dimple, or the sinus may terminate in a cystic swelling in the scalp as in the case presented here. It is situated in the midline either over the occiput or over the bridge of the nose.

On close inspection hairs may be seen protruding from the mouth of the sinus.

Intracranial dermoid cysts occur most frequently in the posterior fossa, but may also occur at the base of the brain or within the ventricles.

In a child with a congenital dermal sinus a plain radiograph of the skull will invariably demonstrate a small bony defect.

Histologically the cyst wall is made up of squamous epithelium. The contents may be hair, teeth, bone, sebaceous material, masses of squamous epithelium and cholesterin crystals.

Complications frequently occur and fall into two groups: (1) The dermal sinus forms a natural tract, which allows infection to enter the central nervous system resulting in either an intracranial abscess or meningitis. (2) The intracranial cyst may enlarge and cause direct pressure effects on the brain, or it may cause signs and symptoms of raised intracranial pressure.

With regard to the treatment Matson and Ingraham (1951) state 'The treatment of choice is surgical excision of the entire dermal sinus tract from the skin surface to its deepest projection, including all cystic expansions, before infection has occurred or at least at a time when no infection is present'.

In the case presented here there was also the Klippel-Feil deformity. This is known to be associated with other congenital abnormalities of the central nervous system, among which Illingworth (1956) has mentioned 'cholesteatoma' of the cerebellum. This tumour is now considered to be epidermoid in origin.

Summary

A case of recurrent meningitis due to an infected intracranial dermoid cyst is reported. The condition was associated with a congenital dermal sinus and the Klippel-Feil syndrome.

In any obscure case, and particularly any recurrent case of meningitis, it is recommended that a careful search should be made for any evidence of a congenital dermal sinus.

I wish to thank Dr. C. G. Parsons for permission to publish this case, and Mr. E. Turner for details of the operation and for his helpful advice. I should also like to thank Dr. K. B. Rogers for the bacteriological investigations, Dr. R. Astley for the radiographic findings, Dr. A. H. Cameron for the histological reports, Mr. J. G. Williamson for the photographs and Mr. D. R. Paton (Royal Hospital, Wolverhampton) for the photomicrographs.

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SIRENOMELIA: SYMPUS DIPUS ("MERMAID")

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 5, 1957)

Hendry and Kohler (1956) have recently reviewed the condition of sirenomelia, and in view of its rarity it was thought that a further case record would be of value.

Case Record

The mother, a primigravida of 18 years, had a normal pregnancy, she was rhesus negative, and had no antibodies. The infant was delivered as an extended breech on July 6, 1957, four weeks before term, and weighed 3 lb. 14 oz. (1·76 Kg.). Grunting respirations occurred as soon as the child was delivered and these continued for several minutes, while the heart continued to beat for one hour. Immediately after delivery the child cried and the toes were seen to move.

External Examination. At necropsy a well-preserved sirenomelus of uncertain sex, 17½ inches long, was seen (Fig. 1). The upper limbs appeared flattened antero-posteriorly, and the wrist, metacarpo-phalangeal and interphalangeal joints were readily hyperextended. The pelvic girdle was about two-thirds the expected diameter. A small, shallow dimple was present over the top of the coccyx, and another dimple, immediately below it, represented an imperforate anus. External genitalia were not present, nor was there any urethral orifice. The lower limbs were fused in their whole length and were rotated so that the patellae were on the lateral aspect of the leg. Movement at the knee was possible in a forward direction only. The fused feet were inverted, with the soles anterior, the heels posterior, and the great toes lateral. Eight toes were present, but the smallest was in the midline, on the posterior aspect, and was not visible from the front.

The pinnae were misshapen and placed a little lower than normal. They did not contain cartilage.

Internal Examination. The head and neck were normal. In the thorax, a tracheo-oesophageal fistula was present half-way between the larynx and the bifurcation of the trachea. The upper end of the oesophagus ended blindly, and was wider and thicker than the lower part which emerged from the anterior aspect of the trachea and continued normally. The trachea was normal except for the small aperture leading into the oesophagus. The lungs were poorly expanded. The inter-lobar fissures were normal except for the right transverse which was represented by a fibrous band. The thorax was otherwise normal.

In the abdomen, the spleen, pancreas, liver and biliary passages were normal; the only abnormal part of the alimentary canal was the sigmoid colon, which ended blindly in a bulbous swelling lying in the left iliac fossa.

The adrenal glands were large, occupying an area equal

FIG. 1.—Post mortem photograph of sirenomelus.

to that normally occupied by the kidneys. A spherical body, 4 mm. in diameter, situated immediately inferior to the left adrenal gland, was shown histologically to be a rudimentary kidney. No ureters were present but a tubular structure was present on each side below the level of the kidney, attached to a gonad and ending blindly in the skin of the inguinal region (Fig. 2). Histological

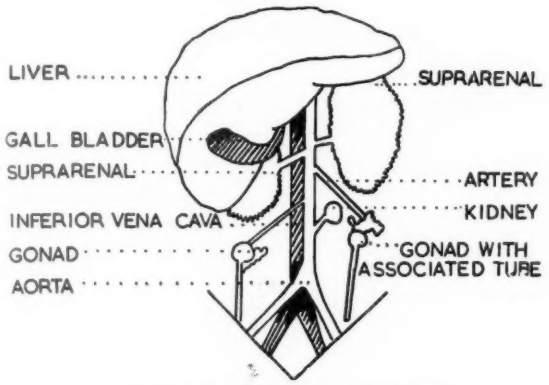

FIG. 2.—Diagram of posterior abdominal viscera.

examination of the gonads showed embryonic seminiferous tubules in the form of solid rods some of which showed early lumen formation, corresponding to the fifth month of development, while cell nuclei examined from several sites showed a female chromatin pattern.

No other pelvic organs were present. The great vessels in the trunk appeared normal, but there was only one artery in the umbilical cord.

MUSCULATURE OF PELVIS AND LOWER LIMBS (Fig. 3). The only internal pelvic muscles present were iliacus and psoas on either side. An unidentified muscle ran between the two greater trochanters. Muscle fibres, arising from both surfaces of the transverse processes of the lower three segments of the sacrum, fused just inferior to the tip of the coccyx, to form a median muscle, whose tendon was inserted into the morphological lateral condyle of the right tibia. The hamstrings were absent. The quadriceps attachments were normal except for an extra branch of the patellar tendon on the left, which ran infero-medially, to be inserted into the tarsus. The deeper fibres of vastus lateralis formed a cruciate arrangement posterior to the knee-joint, and a few of these fibres formed a slender median muscle, whose tendon was attached to the tarsus. The anterior tibial group of muscles (on the posterior aspect of the lower limb) was abnormal and no muscles arose from the anterior aspect of the lower legs. An interosseus muscle arising from the central fibula ran laterally to each tibia.

Radiographic Examination (Fig. 4). The head, neck and upper limbs were normal. There were seven cervical vertebrae, 13 thoracic vertebrae and paired ribs, and six lumbar vertebrae, five sacral segments directed more posteriorly than usual, and a coccyx. In the pelvis, a median bony ridge represented the fusion of the right and left conjoined rami of the ischium and pubis, thus causing the acetabula to face postero-laterally. In the conjoined lower limbs, two separate femora and two tibiae were present, while a median bone, equal in width to the tibiae, lay posterior to them and was thought to represent a fusion of the fibulae. Three centres of ossification were seen in the tarsus, and eight toes were present.

Discussion

In sirenomelia, the developmental abnormality in the lower limbs appears to be a failure of the medial rotation which normally takes place in foetal life. Consequently the anterior aspect of the limb is directed laterally and the fibulae come to lie medial and posterior to the tibiae. This medial position of the fibulae is a characteristic finding in the condition and in our case there is only a single median bone which from its width and muscle attachments is thought to represent a fusion of the fibulae. The failure of rotation causes the soles of the feet to be directed anteriorly and the great toes to be on the lateral aspect of the feet, and results in the peculiar fish tail shape of the fused feet. There is similar failure of rotation of the thighs so that the greater trochanters are directed posteriorly.

Malformations of the urinary tract are usual in

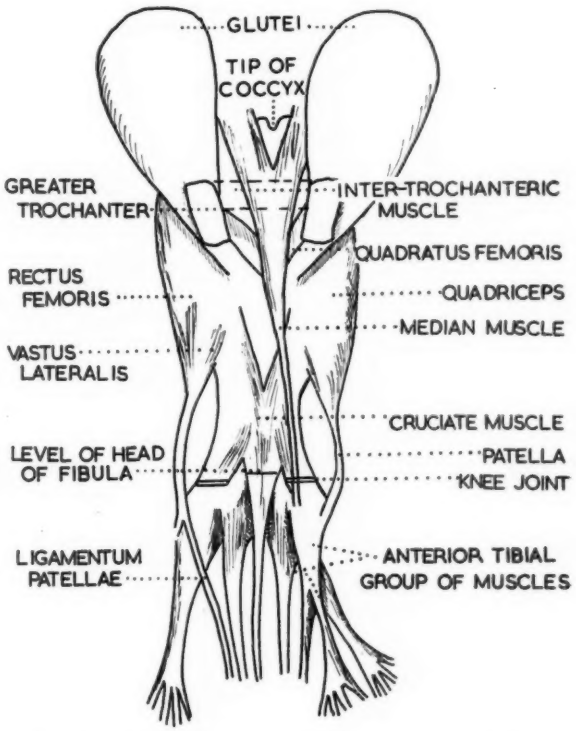

FIG. 3.—Diagram of musculature of pelvis and lower limbs.

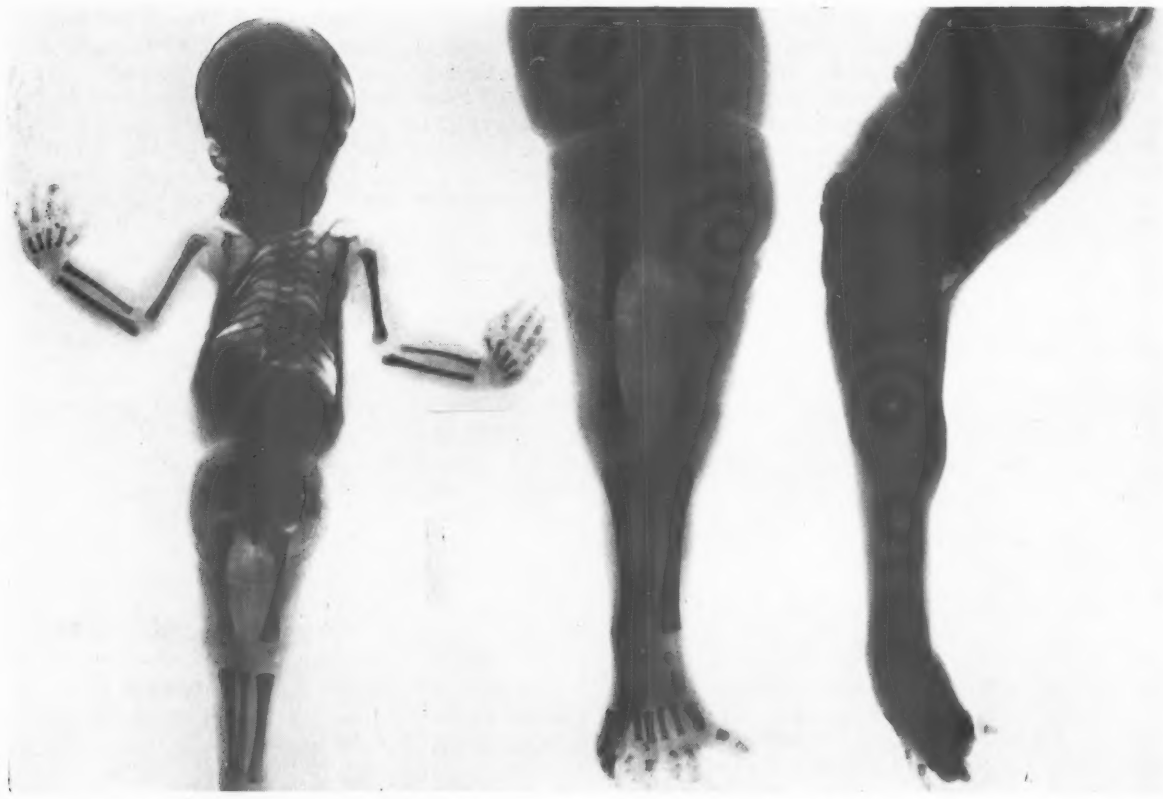

FIG. 4.—Anterior and lateral radiographs of skeleton. The extra vertebrae, the median pelvic bone, the posterior tilt of the sacrum, the posterior fused fibulae, and the fused feet are well shown.

this condition and in this case the only existing part of the urinary system was a single rudimentary left kidney.

Contrary to popular mythical beliefs, the majority of infants with sirenomelia have male gonads as in this case. The nuclear chromatin pattern is less specific to the condition so that little can be deduced from the fact that the pattern was female.

In this case, as in others, only one artery was present in the umbilical cord, while an added feature was the presence of a tracheo-oesophageal fistula.

Summary

A further case of sirenomelia is recorded in view of recent interest in the subject.

We are indebted to Dr. M. R. Thomas for assistance with the necropsy. We are also grateful to Detective Constable R. V. Dallen for the photograph and to Chief Constable J. F. Skittery for providing this facility.

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GARGOYLISM: CLINICAL, RADIOLOGICAL AND HAEMATOLOGICAL FEATURES IN TWO SIBLINGS

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 5, 1957)

Gargoylism is a rare disease. The complete form of this condition is easily recognized, but incomplete cases occur, and some of these are confused with the Morquio-Brailsford type of chondro-osteo-dystrophy. Most of the recorded cases have been in infants and children, and the early manifestations of this disease are well described by Caffey (1952). Fairbank (1951) states that, as a rule, gradual deterioration takes place and that the child dies before growth is complete. The expectation of life is much greater in incomplete varieties. Lindsay (1950) emphasizes the frequency with which the cardiovascular system is involved. The average age of gargoyle patients dying of cardiac failure is approximately 11 years, with a range of from 1 to 29 years. Cardiac hypertrophy is a striking feature, and there are pronounced lesions in the valves and the coronary arteries. He states that extra-cardiac factors probably contribute to cardiac embarrassment. The most important of these are thoracic deformity and chronic interstitial pneumonitis; the latter appears to be secondary to chronic naso-pharyngeal inflammation. Extensive reviews of the clinical and radiological features of this condition are available. It is therefore unnecessary to repeat them.

The two cases to be reported seem to be the first described in non-whites in South Africa. The only cases previously reported from South Africa by McDonald and Opie (1951) and Jackson (1951) have been in individuals of European extraction. Townsend-Coles (1955) has noted three cases in children of the Northern Sudan.

Case Reports

Case 1. An Indian male, known as 'Tweedledum', was first admitted to King Edward VIII Hospital on August 30, 1954, at the age of 11 years. He was of stunted growth, height 3 ft. 8 in. (Figs. 1 and 2). He was deaf and dumb, but of a happy disposition. He had a large dolichocephalic type of head on a very short neck. The facies were heavy, with a depressed bridge to the nose. His respiration was snorting, with open mouth, and he had a profuse nasal discharge. The tongue constantly protruded: the tricuspid teeth were irregular and not in a straight row. The abdomen was protuberant, with everted umbilicus. Hirsutes was evident. There was gross hepatomegaly, but no splenomegaly. He could not extend the elbows freely, and could not raise the arms straight above the head. Flexion of all joints was full. The hands were claw-like. There was no obvious spinal deformity. Reflexes were all present, and motor power was good. There was no clouding of the cornea. The fundi were normal. There was no cardiomegaly; the pulse was 80 and regular. The heart sounds were closed.

LABORATORY EXAMINATIONS. The cerebrospinal fluid was normal. The serum cholesterol was 173 mg. %. The serum calcium was 11·1 mg. %. The serum alkaline phosphatase was 19 K.A. units. Kolmer complement fixation tests on blood and cerebrospinal fluid were negative. The haematological features will be discussed separately.

Case 2. An Indian male, known as 'Tweedledee', was aged 10 years at the time of admission with his brother and was slightly taller. He had an identical configuration, and exhibited very similar features. Hirsutes was marked (Figs. 1 and 2). He was mentally alert, showing an eager interest in his surroundings and was always the instigator in the two's activities. He exhibited night blindness. He was not completely deaf, and was able to speak, though not very distinctly. There was no clouding of the cornea and the fundi were normal. He had signs of upper respiratory catarrh. There was no cardiomegaly.

Laboratory findings were very similar to those of his brother and were non-contributory.

Radiological Features

These were almost identical in the two siblings. The radiographs illustrated are those of Case 1.

Skull. This showed some degree of hydrocephalus, with a dolichocephalic configuration. The pituitary fossa

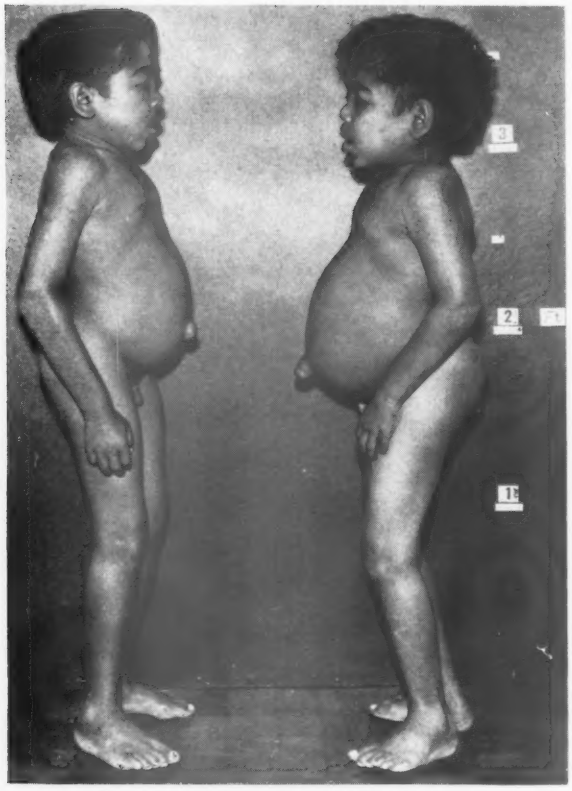

FIG. 1.—The brothers, aged 10 and 11 years.

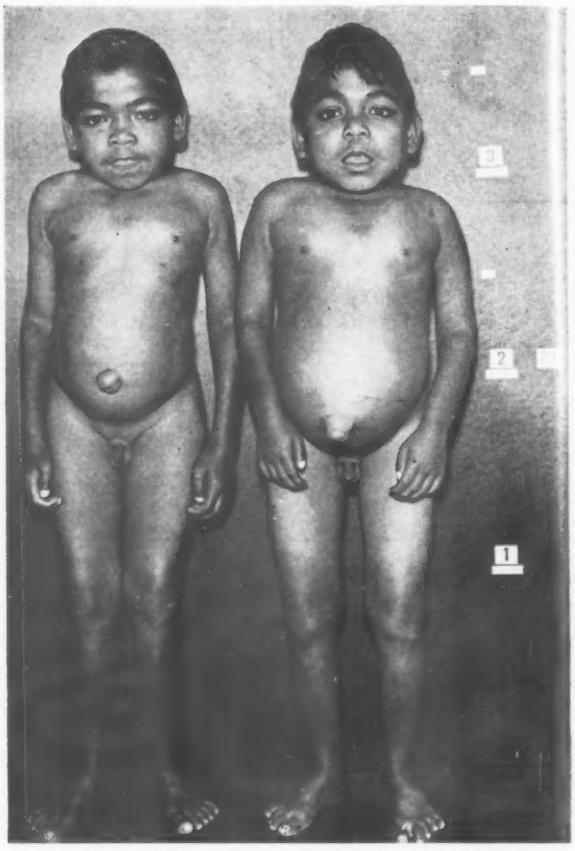

FIG. 2.—The brothers, at the same age as in Fig. 1.

was not obviously enlarged, but the posterior clinoid processes were long (Fig. 3). There was some bulging of the temporal regions. The mandibles appeared slightly enlarged.

Spine. Some of the dorso-lumbar vertebrae were biconvex, and a few vertebrae showed very slight beaking at the lower anterior angles. There was no abnormal kyphosis, and no hypoplasia of the vertebral bodies.

The ribs appeared thicker than normal. The glenoid fossae were shallow.

Upper Limbs. The long bones appeared somewhat tubular, the diaphyses being about the same width as the metaphyses. There was bowing of the radii, and the distal ends of the metaphyses of the radii and ulnae sloped towards each other. Ossification of the wrist bones and carpal bones was delayed. The metacarpals and phalanges were tubular, with a thin cortex, and there was slight pointing of the proximal ends of the metacarpals. The terminal interphalangeal joints of both hands were flexed (Fig. 4).

Lower Limbs. The capital femoral epiphyses were flattened, and there was a coxa valga deformity. The acetabula did not appear shallow. The cortex of the

FIG. 3.—Dolichocephalic skull, with elongated posterior, clinoid processes.

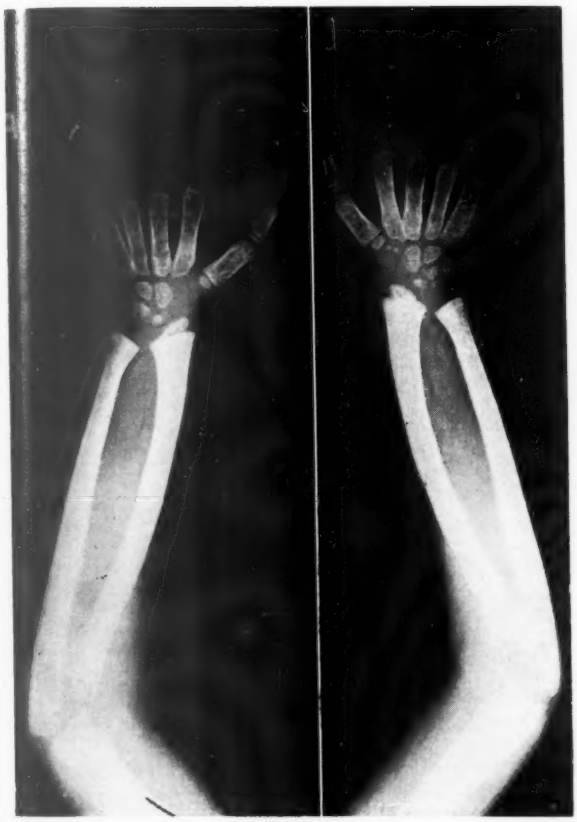

FIG. 4.

lower ends of the femora was thinned and the bones had a shape similar to that seen in Gaucher's disease. The feet showed slight changes similar to those of the hands.

Heart and Lungs. There was some increase of the pulmonary vascular shadows, and prominence of the pulmonic arc. There was no enlargement of the heart at the first examination (Fig. 5). On re-examination approximately two years later cardiomegaly was demonstrated, with marked increase in the prominence of the pulmonic arc, suggesting cor pulmonale (Figs. 5 and 6).

Although the clinical features of these cases are well developed and diagnostic, the radiological features are relatively slight. Retardation of growth is not marked. The upper limbs are not shortened, and the degree of deformity of the shafts of the long bones is not striking. The vertebral changes are very much less obvious than in many reported cases. All the findings, however, are in conformity with the changes described in gargoylism.

FIG. 4.—Showing the flexed terminal interphalangeal joints, the tubular shape of the phalanges and metacarpals, the pointed bases of the metacarpals, the abnormal slope of the distal metaphyses of radii and ulnae and bowing of radii.

FIG. 5.—No cardiomegaly; slight increase of the pulmonary vascular shadows and slight prominence of pulmonic arc.

FIG. 6.—Cardiomegaly with marked increase in prominence of pulmonic arc.

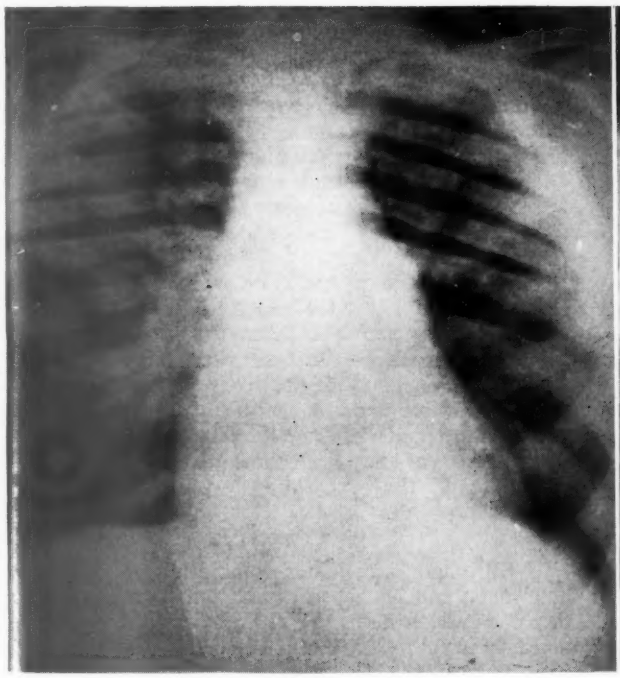

FIG. 5.

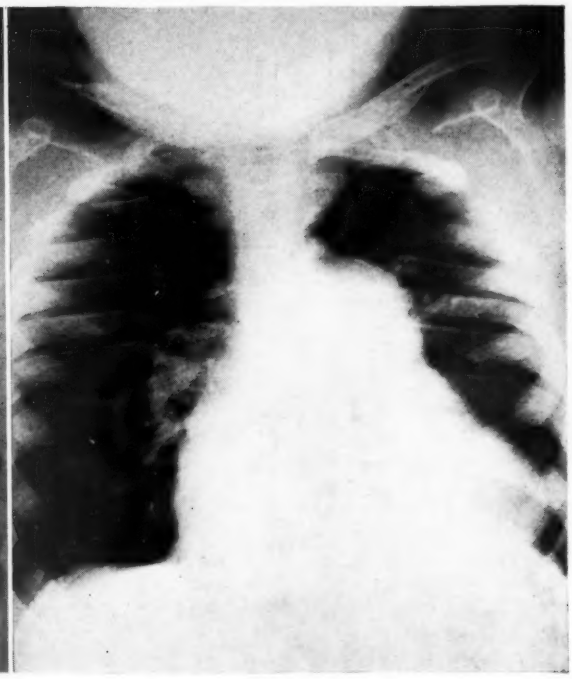

FIG. 6.

Haematological Findings

The peripheral bloods of the two cases were virtually normal. Alder's (1939) anomaly, which consists of a purple staining granulation of the cytoplasm of the polymorphonuclears, lymphocytes and monocytes, was searched for but was not found. This, however, is not surprising as, in spite of some reports, only a moderate number of cases of gargoylism show any abnormality of the white cells of the circulation (McKusick, 1956 ; Reilly and Lindsay, 1948).

Sternal punctures were performed on both patients. Great difficulty was experienced in piercing the extremely tough skin over the sternum, but good samples of marrow were obtained. The marrow particles were of normal cellularity and leucopoiesis and erythropoiesis were normal. Again Alder's anomaly was not observed, in spite of a prolonged search. The most striking feature of the films, which were stained by the May-Grunwald Giemsa technique, was the presence of numerous large cells distended with many very dark purple-staining masses of varying size. These granules, the largest of which were 1-2μ in diameter, almost completely obscured the outline of the cells, and partially obscured the nuclei. Similar masses of granular material were also found lying free, presumably originating from cells ruptured in smearing. The cells containing these granules were considered to be histiocytes and are shown in Fig. 7.

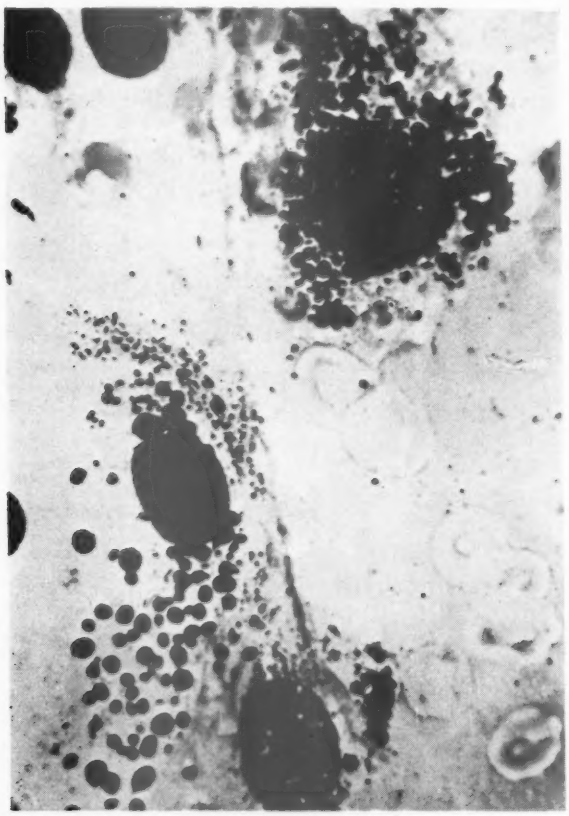

FIG. 7.—Histiocytic cells showing masses of darkly staining material. This resembles the type of cell described by Gasser.

FIG. 8.—Ring-like bodies in clear vacuoles found in cytoplasm of plasma cells.

They were found in the marrow of both patients and are considered to be identical with those described in a case of gargoylism by Gasser (1950).

In addition to this abnormality, further extraordinary inclusions were observed. They were dark purple-staining ring-shaped bodies approximately 1μ in diameter with clear centres, which were found in vacuoles in the cytoplasm of cells, believed to be plasma cells. They are shown in a microphotograph (Fig. 8).

We were unable to trace reports of similar findings in the literature, and we consider them to be quite distinct from the inclusion bodies described previously as occurring in gargoylism.

These cells were present in the marrows of both cases. In September, 1956, the bloods of these cases were re-examined by Dr. J. Duncan-Taylor who found the same phenomena in the bone marrow. Attempts to stain the granules and the ring-like bodies using Nile-blue sulphate and the periodic acid-Schiff method on formol vapour fixed material were unsuccessful. At no time was the material allowed to come in contact with alcohol or xylol and the preparations were examined under water.

Progress

The brothers were under observation for two and a half years, and had been in and out of hospital many times. 'Tweedledum', the elder, had three attacks of bronchopneumonia in 18 months, and developed chronic heart failure. He became dyspnoeic at rest. There was slight ankle oedema. The liver was enlarged to the

umbilicus, and there was some enlargement of the spleen. The blood pressure was 120/90 mm. Hg. An electrocardiogram showed right ventricular strain and hypertrophy. The heart became enlarged, with the apex beat in the fifth interspace between the nipple line and the anterior axillary line. There was a blowing systolic murmur at the apex, conducted to the axilla. The pulmonary second sound was accentuated with a soft systolic murmur. He died in March, 1957, from acute cardiac failure. Permission for necropsy could not be obtained.

'Tweedledee', the younger, was always admitted to hospital with his brother because they were inseparable. He has had one attack of bronchopneumonia in the last 18 months. He is not in congestive cardiac failure, and has not developed cardiomegaly. He has dyspnoea on slight exertion. Hepatomegaly is fairly marked, but there is no sign of splenomegaly.

The mother of the children has recently been interviewed, but she was a bad witness, and little information could be obtained as to the earlier history of the siblings. She had two normal children, one about 19 years and the other 9 years old.

Aetiology and Pathogenesis

The aetiology and pathogenesis of this comparatively rare disease is a matter of controversy. The term lipochondrostrophy suggested by Washington (1937) indicated the current view that the disease was a disorder of lipid metabolism associated with skeletal deformities. In a recent review by Creveld (1953) it is still classified amongst the lipoidoses, although current work suggests that the abnormal substance present in the tissues is not a lipoid. The disease was considered to be a lipoid storage disease by Ellis, Sheldon and Capon (1936) and by Henderson (1940).

The essential lesion of the disease is the accumulation, in various parts of the body, of cells containing an abnormal substance, and the bizarre clinical features of the disease can be attributed to the resulting disturbance of structure and function of the affected tissue. The chemical composition of this stored material has been the subject of several recent papers but its nature is still undecided. One of the difficulties is that only a small number of cases have had biopsies or autopsies performed, and no investigator has had material from more than three or four cases to examine. It is possible that the condition is a syndrome which may be caused by the accumulation of more than one substance, thus accounting for the varying results reported. This would also account for the variation in the clinical features of some reported series; and there is increasing recognition of 'incomplete' forms, some of which can only be differentiated with difficulty from similar conditions such as Morquio-Brailsford disease (Kammerer, Mathis and Wackenheim, 1955).

The injection of macromolecular substances of varying chemical nature into experimental animals can produce extensive anatomical changes (Hueper, 1942) but so far the syndrome of gargoylism has not been produced.

Lindsay, Reilly, Gotham and Skahen (1948) thought that the stored material in gargoylism was a glycogen-protein complex. Brante (1952), in a study based on three cases in which he isolated a lipid and a non-lipid fraction, thought the disease was mucopolysaccharidosis. Uzman (1955) reported the isolation of a polysaccharide and a glycolipid fraction. He considered the disease was not caused by the accumulation of these substances, but as a result of a defect in the synthesis of polysaccharide which is known to be intimately concerned with the synthesis of collagen.

Even if it is accepted that the symptomatology of the disease is due to a metabolic defect, there is also evidence that hereditary factors are important in its development. The usual influences which increase the incidence of foetal abnormalities have not been shown to operate in this disease. Maternal age, trauma, disease or state of parity are unimportant. An endocrine factor functioning either directly or as a potentiating influence has been suggested by some (Kammerer *et al.*, 1955), but there is little to substantiate this. Most authors agree that there is a high incidence of families with more than one affected child. Lindsay *et al.* (1948) cite the family described by Böcker (1943) in which there was an affected child in each of four generations who were direct descendants of one unaffected woman. There was also one girl showing signs of Morquio disease in the third generation. Halperin and Curtis (1942) considered that the occurrence of affected individuals could be explained by its being determined by a single autosomal gene. Jervis (1950) in whose series 26 of the 85 families studied had two or more affected members, considered that the numbers were consistent with the condition being due to a single recessive gene. This would only hold if there was a high incidence of cousin marriages. In 11 of 103 families the parents were cousins. A sex linked form has been described (Millman and Whittick, 1952) and single members of binovular twin pairs have been affected, while the other twin has been unaffected. (Lindsay *et al.*, 1948). There is thus strong evidence for gargoylism being a hereditary defect, and McKusick (1956) goes as far as to say that there are at least two genotypes of this disease which can be distinguished clinically.

The two cases described show a remarkable similarity to each other, but whilst the clinical picture closely resembles the classical descriptions

of the disease, the radiological features are less marked than might be expected. The blood findings, too, are unusual, and have not hitherto been described. This again emphasizes the probability that different types of the disease exist. Possibly there are different underlying mechanisms which can produce closely similar syndromes.

Summary

Gargoylism in two brothers is described. They appear to be the first cases of this condition recognized in individuals of Indian extraction. The clinical, radiological and unusual haematological findings are described and discussed. Granular inclusions in the bone marrow histiocytes were present, and hitherto undescribed ring-shaped inclusions were present in the plasma cells of the bone marrow.

We wish to thank Dr. S. Disler, Superintendent of King Edward VIII Hospital, for permission to publish these cases, Dr. Rossiter, under whose care they were admitted, and Mr. C. R. Stuart, of the Department of Pathology, University of Natal, for the photographs.

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HYDRANENCEPHALY (HYDRENCEPHALY)

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 30, 1957)

The terms 'anencéphalie hydrocephalique' and 'hydroanencéphalie' were first used by Cruveilhier (1829, 1862), although the condition appears to have been described even earlier by Breschet (Breschet, 1823, quoted by Kobelt, 1938). The designation was later abbreviated to 'hydranencephalie' ('Hydranenkephalie' in its original German spelling) by Kluge (1902) and Spielmeyer (1905). The subject has been reviewed by Lange-Cosack (1944) and, more recently, by Moser (1952), who collected 32 recorded cases. Many authors still refrain, however, from using the term, presenting similar cases as 'hydrocephalus', 'ox-bladder brain', 'Rindenblasen-porencephalie', 'hydro-microcephaly', 'porencephaly', 'schizencephaly', and so on. Some of the current textbooks do not even mention 'hydranencephaly', while, on the other hand, new cases are being reported (Watson, 1944; Hamby, Krauss and Beswick, 1950; Najman, 1953; Thelander, Shaw and Piel, 1953; Olive and Du Shane, 1953; Hallervorden and Meyer, 1956).

In this condition the cerebral hemispheres are replaced by thin-walled sacs containing cerebrospinal fluid. Its extreme form is incompatible with prolonged survival, and most of the reported cases have been either stillborn or children dying in early infancy. One of the two cases presented by Lange-Cosack, living to 1 year, was allegedly the oldest on record.

While few of these young infants are likely to come under the care of mental deficiency authorities, some, with 'partial hydranencephaly', if such a term be permitted, may live longer and be seen more frequently with low-grade mental defect. We feel justified, therefore, in reporting the following case of hydranencephaly which occurred in a consecutive series of 300 autopsies performed chiefly on low-grade mentally defective children at the Fountain Hospital. If not extreme, the condition may be difficult or impossible to differentiate from related encephalopathies, particularly from hydrocephalus, and this is illustrated by a brief presentation of two further cases, showing some features of hydranencephaly.

Case 1. The patient, the first-born child of healthy parents aged 25 and 24 with no family history of mental or neurological illness, was delivered normally after a pregnancy lasting eight months. He weighed 2·8 kg. at birth and was apparently normal. He developed a cold on the third day and it was noticed then that he never slept more than a few hours at a time.

Constant screaming and the fact that the patient 'took no notice' by the time he was 3 months old caused the parents to seek advice. His head circumference was then 33 cm. with the fontanelle slightly bulging even when not crying. The muscle tone in the limbs, but not in the neck and back, seemed good. The eyes tended to deviate downwards and to the right and the pupils reacted sluggishly to light. Fundal examination, difficult in the circumstances, revealed scattered discrete pigmentation. The left disc was pale and there was a large pale patch near the right disc. He failed to pass any of the usual milestones of development—sitting, crawling, standing, talking or gaining sphincter control. The head gradually increased, never exceeding, however, the limits of normal —42 cm. at 2 years.

Home care became increasingly difficult and he was admitted to the Fountain Hospital at 2 years 9 months, when he was assessed as an idiot with a mental age of 1 month. He weighed 11·4 kg. and lay supine and helpless in his cot. The anterior fontanelle was patent but the skull was normal in shape and size. He could move his limbs and often bit his hands till they bled. Muscle tone was increased in the legs; the knee and ankle jerks were present and both plantar responses were extensor. The abdominal reflexes were absent. He was apparently blind and had marked nystagmus. Both pupils were semi-dilated and reacted sluggishly to light. Ophthalmoscopy confirmed the previous findings of retinal scarring with multifocal pigmentation. His hearing was doubtful. Cardiovascular, respiratory, alimentary and genito-urinary systems were normal.

Routine laboratory investigations such as the W.R., Mantoux and toxoplasmin skin tests were negative. (No other serological tests for toxoplasmosis were done.) Radiological examination at 3 years 9 months showed osteoporosis of the sella turcica and non-united cranial sutures. Later he was found to have a congenital dislocation of the left hip.

During his 18 months' stay in hospital he had several episodes of respiratory infection, vomiting and diarrhoea, and developed measles. He also suffered from petit mal

attacks which gave way later to major fits, mostly diurnal, occurring two to four times a month for the last ten months of his life. He made no mental or physical improvement and died of bronchopneumonia at 4½ years.

Pathological Findings

Necropsy. The subject was an extremely dehydrated and emaciated boy weighing 8·9 kg., with regular features and a profuse growth of fine hair over the face and trunk. The head measured 50·5 cm. in circumference. A naevus was present on the left calf, but there were no other external deformities. The trachea and bronchi contained thick secretion and the lungs showed hypostatic congestion, and focal consolidation with 'geographical' surface markings. A few petechiae were present on the pleural surface. All other organs, excepting the brain and eyes, appeared normal.

Microscopical examination of the lungs revealed a combination of lobular collapse with partial infective atelectasis, and inhalation pneumonia. Some alveoli adjoining the areas of collapse were filled with amorphous debris, others contained phagocytic cells of varying size. These had small, darkly-staining nuclei and irregularly outlined, sometimes enormously distended, vacuolated and reticulated cytoplasm. Plasma-cell infiltration was present round the margins of some of the areas of collapse and inhalation pneumonia.

Central Nervous System

The cerebral hemispheres were incised on opening the skull and it was therefore impossible to ascertain whether any of the considerable amount of fluid was subdural. The brain (Fig. 1), emptied of cerebrospinal fluid, weighed 210 g. The left cerebral hemisphere (13·5 × 9 × 5·2 cm.) was represented over the greater part by a paper-thin, transparent sac, marked on its surface by attenuated blood-vessels. Only the posterior and basal portions of the occipital and temporal lobes were more solid, measuring up to 0·4 cm. in thickness. The right hemisphere was better preserved. Its medial surface was also paper-thin, but the rest averaged 0·8 cm. in thickness. While the thinnest parts of the hemispheres were smooth, more solid areas presented a characteristic microgyric pattern, varying from flat 'morocco-leather' to coarser 'cobble-stone' markings. Where it could be measured, the ratio of grey to white matter was about 2 to 1. The internal surface of the hemispheres was smooth and glistening, showing, however, many irregularly distributed nodular elevations of up to 0·2 cm. in diameter. The distended ventricles communicated by a circular central opening (Fig. 2), 4·3 cm. in diameter, the anterior margin of which was formed by the thin fornices. The corpus callosum could not be identified. The basal ganglia were recognizable, the caudate nucleus being relatively large. A thin, elongated connexus thalamicus was stretched across the greatly dilated third ventricle.

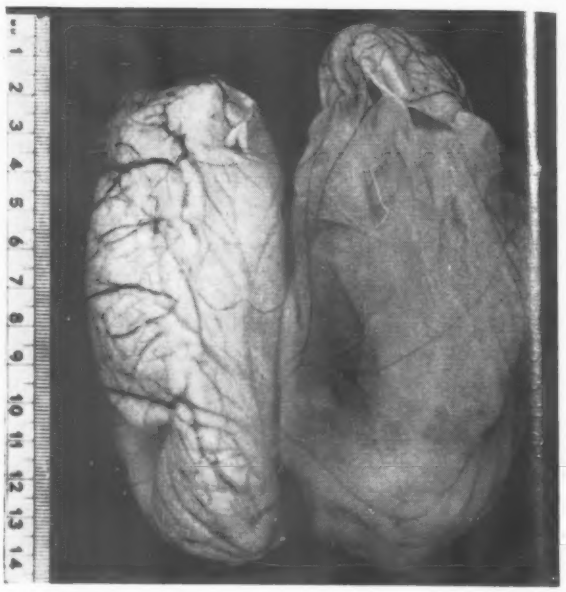


FIG. 1.—Case 1: dorsal view of brain with attenuated vessels on the surface of a dilated and diaphanous left ventricle which has been distended with a balloon.

The cerebellum, flattened from above downwards, was

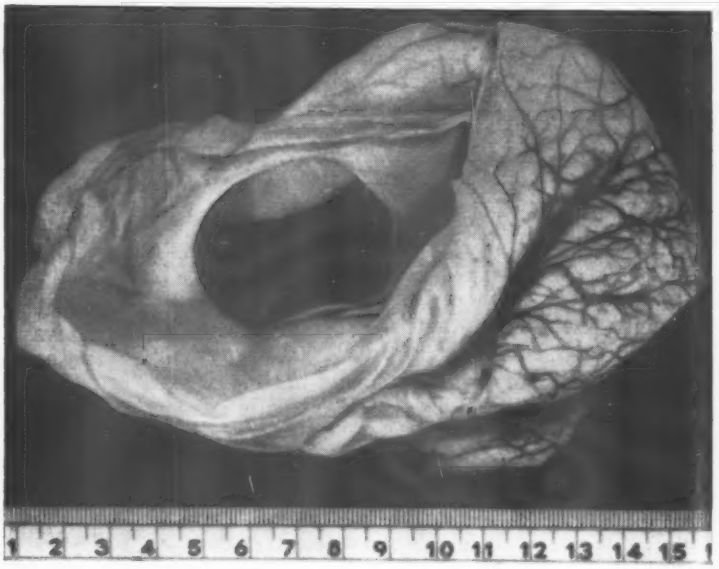


FIG. 2.—Case 1: a large foramen of Monro and dilated lateral ventricles revealed through an incision in the left cerebral cortex.

small, weighing with the brain-stem 42·0 g. The pattern of the arbor vitae was blurred and many folia were narrow. In the brain-stem, the aqueduct of Sylvius was minute and the pyramids absent. The blood-vessels, cranial nerves (with the exception of the optic nerves) and the spinal cord appeared to be normal.

The Eyes. The eyes (Fig. 3), equal in size, measured 2·2 cm. in diameter. Both showed pronounced, cupped macular scarring with pigmentation in and around the scars. Each of the macular scars was larger than the disc, showing 'grease-spot' translucency when held to the light. Scattered pigmentation and smaller scars were also present elsewhere, being more marked in the temporal halves of the globes. The cornea, anterior chambers, irides, ciliary bodies and sclerae seemed normal. The optic nerves were small.

Microscopy

After prolonged fixation in formalin, representative blocks of the cerebral hemispheres, basal ganglia, brain-stem, cerebellum and spinal cord were embedded in celloidin and in paraffin. Sections were stained by the usual neurological and general histological methods. Frozen material was also used as required.

The meninges were essentially normal. Arteries were thin-walled in the subarachnoid space over the hydranencephalic areas, and slightly thickened over the more solid parts of the brain. The external part of the cortical molecular layer was densely gliosed and showed capillary proliferation in some of the better preserved parts (Fig. 4), the glial cells and fibres tending towards parallel orientation to the surface. In places, the glial tissue projected ridgewise into the subarachnoid space.

The cytoarchitectonic structure of thicker portions of the cortex may be summarized as follows. It was most normal in the hippocampus where the molecular and pyramidal-cell layers, the alveus and fascia dentata were clearly identifiable. The arrangement elsewhere was greatly disturbed, bearing no relation to normal lamination. Some areas showed

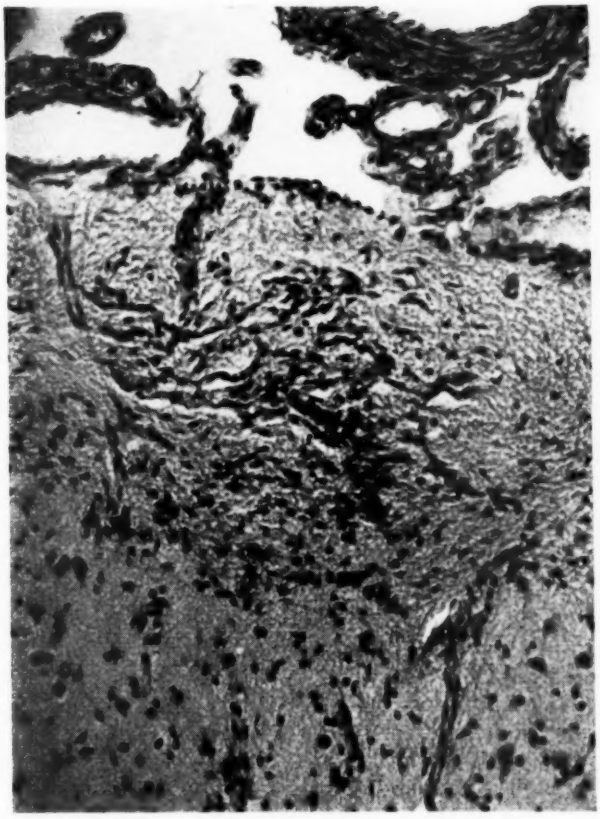


FIG. 4.—Case 1: the external molecular layer of the cortex with glial fibres arranged parallel to the surface. Haematoxylin and eosin × 200.

FIG. 5.—Case 1: cortical microgyria. Haematoxylin and eosin × 30.

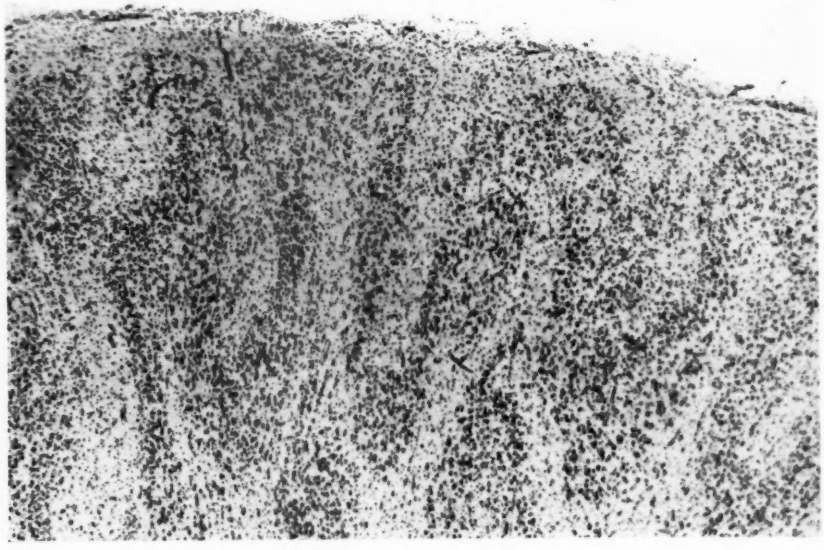
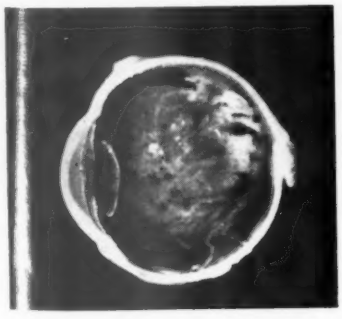


FIG. 3.—Case 1: macular scarring and scattered pigmentation × 3.



true microgyria (Fig. 5), the superficial garlanded neuronal layer being separated from the deeper grey matter by a sparsely cellular layer. The pattern elsewhere was greatly irregular, defying identification and concise description. Nerve cells varied from area to area: some, in the garlanded superficial microgyric layer were medium-sized pyramids, others were small pyramidal or pleomorphic. Nissl substance stained poorly or not at all. Small delicate bundles of myelinated nerve fibres projected from the main mass of the white matter into the central areas of the microgyric convolutions where these were identifiable. Many irregularly orientated ectopic nerve cells were present in the white matter, forming in its deeper portions small clusters or larger islets, and, particularly near the ventricles, a continuous layer (Fig. 6). These heterotopic

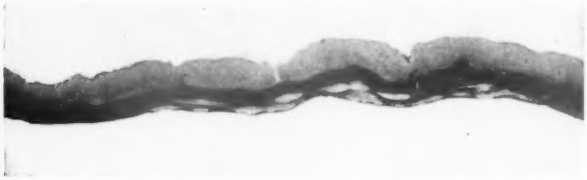


FIG. 6.—Case 1: ectopic grey matter. Heidenhain × 5.

formations of grey matter accounted for the nodular naked-eye appearance of the internal surface of the cerebral hemispheres. Here many of the heterotopic nerve cells showed shrinkage with pyknosis of nuclei and accentuation of dentritic staining. The white matter contained also, near or at the ventricles, many islets and layers of glial cells interspersed densely with particles of calcium (Fig. 7). The latter were mainly extracellular, varying greatly in size. The smallest were dustlike, about 1μ in size, while the largest measured up to 20 to 30μ.

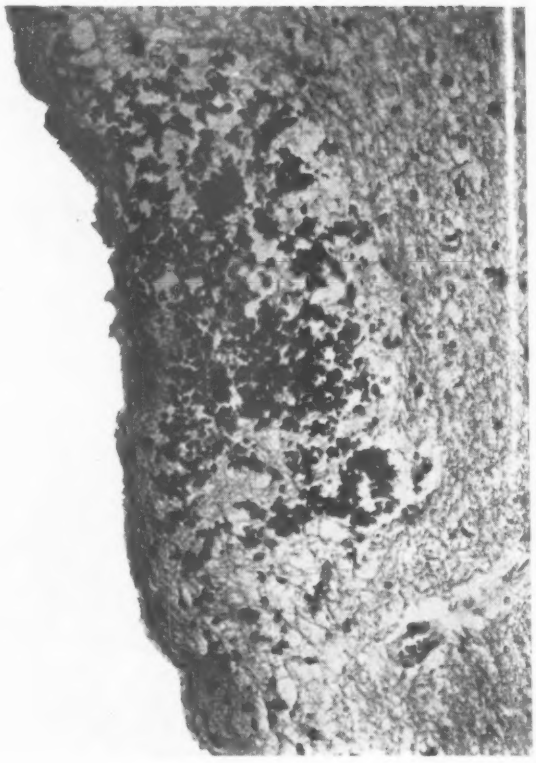


FIG. 7.—Case 1: periventricular calcification. Haematoxylin and eosin × 200.

Most of the ventricular lining, entirely devoid of ependyma, was formed by 12 to 15 rows of glial cells and fibres. In appropriately stained sections this layer showed fibrous gliosis, which was also severe throughout the white matter, particularly in and around the calcified foci, and, as mentioned already, in the sub-pial cortical layer.

The only neutral fat seen was in a few compound granular corpuscles situated in the perivascular spaces, and in some endothelial capillary cells.

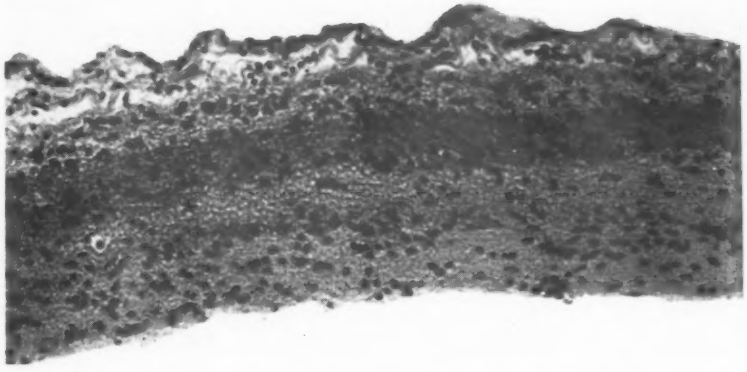


FIG. 8.—Case 1: the cortical membrane composed of partially fused meninges with gliosed cortex. Neurones and ependyma are absent. Haematoxylin and eosin × 200.

The membrane (Fig. 8) enclosing most of the left and a large part of the right hemispheres was formed by partially fused soft meninges externally and a thin uniform layer of glial tissue internally. No stratification of this glial layer could be discerned in thin sections but a certain pattern was visible in appropriately stained thicker sections of celloidin-embedded material. Here the most superficial layer contained few cells and this was followed by a more cellular glial zone, containing also occasional larger degenerate-looking nerve cells and a few compound granular corpuscles. Scanty fragmented and ballooned myelin fibres coursed tangentially in the subjoining layer, which was succeeded internally by irregularly arranged glial cells and fibres. The internal surface was straight and even, showing in a few places foci of linear condensation of four to 10 glial cells.

The basal ganglia were compressed against the base of the skull and the upper part of the striate bodies displaced laterally, presenting, however, little histological abnormality. Normal ependyma lined the entire ventricular system below a point corresponding to the middle of the thalamus. A few ependymal granulations were present. The internal and external capsules were thin on the right side and barely visible on the left. Their myelin stained, however, better than the white matter of the cerebral hemispheres.

Almost the entire cerebellum was microgyric (Fig. 9).

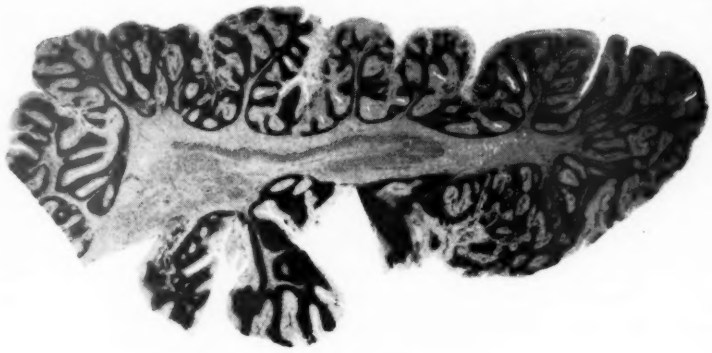


FIG. 9.—Case 1: cerebellar microgyria. Heidenhain × 3½.

Straight or slightly curved tapering streaks of granular and Purkinje cells budded and branched near the surface from stouter and more normally formed folia. Owing to tangential cutting, layers of Purkinje cells were often multiple. The white matter of the cerebellum showed diffuse fibrous gliosis, particularly heavy close to the fourth ventricle, but the dentate and roof nuclei seemed well preserved.

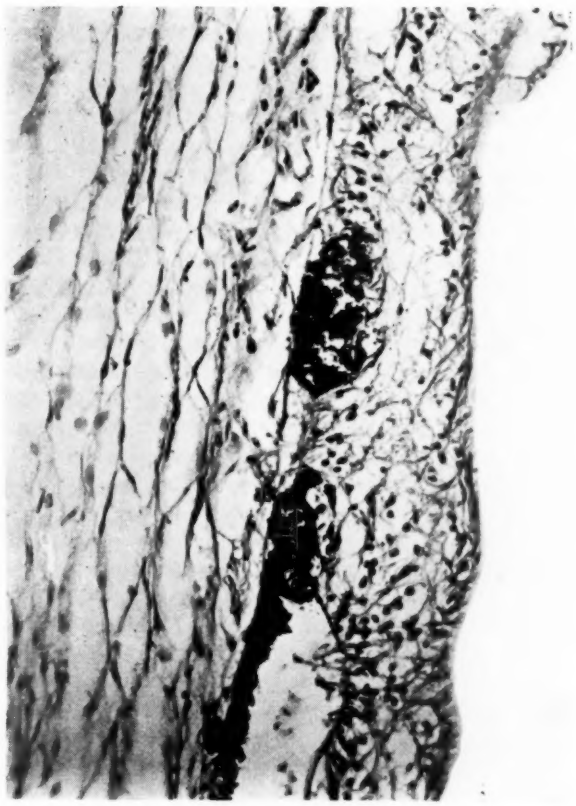
The cerebral peduncles, cortico-pontine fibres and medullary pyramids were rudimentary. The nuclear formations of the brain-stem seemed well developed. A diffuse, fine fibrous gliosis was present throughout the brain-stem, which was most marked around the ventricular and external surfaces. The aqueduct was elongated antero-posteriorly and split into an anterior smaller and posterior larger channel by a bridge of glial tissue in its narrowest portion. Here the widest diameter measured 0·27 mm. and the channel was surrounded by a dense ring of fibrous glia. The constricted portion of the aqueduct widened rapidly with the approach to the considerably dilated fourth ventricle.

The spinal cord showed also diffuse fibrous gliosis, the grey matter being particularly affected. The lateral columns were narrow but showed no discrete areas of demyelination.

Eyes. The retinae and choroid showed widespread focal atrophy varying in extent and severity. Areas of extreme degeneration (Fig. 10) were represented merely by a loose meshwork of fibres containing a few glial cells, with, perhaps, some granules of pigment in the choroid. Moderate degeneration was more extensive, and some normal structural components were usually recognizable in these areas. The retina here was reduced in width, ganglion cells scarce and one or both the nuclear layers depleted of cells. The degree of pigmentation varied greatly, but there was no direct relation between atrophy and pigmentation, some of the most severely degenerated areas showing little or no pigment. The pigment, where present, was mostly extracellular being situated mainly in the external retinal and internal choroid layers, often filling completely elongated spaces. Smaller collections of pigment could also be seen occasionally in the more internal retinal layers. No inflammatory reaction or organisms were present in any of the numerous sections examined.

The neural funiculi of the optic nerves were narrow, and the pial septa thickened.

FIG. 10.—Case 1: retinal atrophy and pigmentation. Haematoxylin and eosin × 200.



Discussion

Morphology. The size of the hydranencephalic cerebral hemispheres has been inconstant in recorded cases. Some, particularly of older patients, have been large, others normal or frankly micrencephalic. The cardinal feature is absence of all or the greater part of solid cerebral tissue. Where any remains, it is usually found in the basal aspects of the occipital and temporal lobes. This was explained by Lange-Cosack by the greater participation of the vertebral, as contrasted with the carotid arteries, in the supply of these areas. The basal ganglia and the rostral parts of the mid-brain are also absent or degenerate in the most severe cases. Formations below this level are usually substantially intact, showing merely agenesis of the long descending tracts. An exception was cystic change in the cerebellum in a case published by Thelander *et al.* (1953).

The meninges, hydranencephalic membrane and remaining brain tissue are often frankly haemorrhagic, reddish or brownish in colour, showing haemosiderin pigment histologically. Proliferation of phagocytic and meningeal cells, and the presence of fibrin, leucocytes and glial cells have also been noted in some cases.

The histological structure of the membrane enclosing the cystic hemispheres is regarded as crucial in differentiating hydranencephaly from hydrocephalus. In hydranencephaly it is formed externally by the arachnoid and pia and internally by a thin layer of glial tissue said to be devoid of nerve cells, axis cylinders or ependymal lining (Lange-Cosack, 1944; Peters, 1951; Moser, 1952), some neural parenchyma being preserved even in extreme instances of hydrocephalus. However, this criterion may not be conclusive. Russell (1949) describes a membrane in hydrocephalus caused by focal herniation of the ventricular wall through one of the deeper cerebral outer sulci with wide separation of the bordering convolutions. This membrane, partly denuded of ependyma, appeared to resemble that in hydranencephaly, although strips of ependymal cells were present in that case.

Some of the earlier workers also found a few degenerated nerve cells in the hydranencephalic membrane (Kluge, 1902; Spielmeyer, 1905; Kobelt, 1938). Moreover, the demonstration of nerve cells and their processes depends partly on the methods employed. While none could be seen in the thin sections of the paraffin-embedded material in our case, other areas embedded in celloidin and cut more thickly showed unequivocal evidence of nerve cells and myelinated nerve fibres. The absence of ependymal lining is likewise regarded as evidence that the membrane is not formed as in hydrocephalus by the peripherally displaced ventricular wall. This, again, may not be unequivocal. The ependymal lining is, as mentioned already, often partially shed in cases of hydrocephalus, and the ventricular wall can be identified in its absence by the characteristically stratified arrangement of glial cells and fibres in such areas. This was clearly present over a large part of the internal surface of the membrane in our case. A condition, similar to human hydranencephaly was, moreover, described in newborn and stillborn calves by Whittem (1957). He found that the membrane in these cases was formed externally by meninges and internally by ependyma, the intervening spaces containing ragged fragments of well-preserved cortical tissue with nerve cells, astrocytes and other elements. It seems, therefore, that although remnants of neural parenchyma are always scarce, they may not be entirely absent in the hydranencephalic membrane. This would depend, presumably, on the degree and duration of the condition.

The fluid in the hydranencephalic hemispheres is usually clear cerebrospinal fluid. It may, however, be turbid or blood-stained, especially in early cases and after ventricular or spinal puncture.

Stenosis around the foramina of Monro was present in one of Lange-Cosack's cases, and atresia of the Sylvian aqueduct in a case described by Watson. In another instance (Hurowitz, 1936), whose classification is uncertain (*vide infra*), there was no communication between the cerebral cysts and the anterior part of the aqueduct, which was split into many narrow channels. Many of the recorded cases have not been fully examined but some block in the cerebrospinal fluid pathway, functional or anatomical, is frequent; thus Beswick (1948) and Hamby and his colleagues (1950) failed to recover in the cerebrospinal fluid obtained by lumbar puncture dye injected earlier into cerebral ventricles in most cases where this procedure was tried. Aqueductal stenosis was present in our case, the lumen being approximately a quarter of the narrowest width of the normal (0·1 cm.) reported by Sutton (1950), but it is uncertain whether this was the sole cause of the accumulation of the fluid above it.

As expected from the relatively long survival, our case showed more preservation of cerebral tissue especially on the right side, than in other recorded instances. It presented, in addition, microgyria, periventricular calcification and chorioretinopathy with pigmentation, the aetiological significance of which will be discussed below. Similar retinal changes were present in two of the hitherto reported cases (Hamby *et al.*, 1950; Beswick, 1948). 'Micro-

gyria' was mentioned by Kluge in his case, but it is impossible to decide from his description whether this was true microgyria, as in ours.

Aetiology, Pathogenesis and Classification. It seems generally agreed that hydranencephaly results from destruction and resorption of preformed solid cerebral tissue commencing before birth. The possible pathogenetic mechanisms have been fully discussed by Lange-Cosack (1944) and Becker (1949), both favouring ischaemia as the mechanism of the condition and Lange-Cosack suggesting further that this follows compression of the foetal carotid arteries by the umbilical cord or amniotic adhesions. Becker was able to produce comparable unilateral changes in newborn puppies by the injection of a mixture of paraffin and olive oil at a melting point of 40° C. into one of the carotid arteries. The ensuing changes were, successively, necrosis, resorption, and, after nine months to one year, smooth-walled cavitation enclosed by a 'hydranencephalic' membrane. He thought that compression of the carotids might lead first to thrombosis, all intra-arterial traces of which would disappear in time. A case of unilateral cystic degeneration associated with recanalized thrombosis of the middle cerebral artery was reported by Meyer (1949). While this may well be the explanation in some cases, it is difficult to reconcile with the lack of mention of arterial thrombosis in any other of the recorded cases. Moreover, cerebral arteries of hydranencephalic infants observed at craniotomy or by means of angiography by Hamby and by Thelander and their colleagues were patent and, apparently, normal. It is certainly difficult to relate the distribution of the changes in our case to any known arterial pattern.

Congenital syphilis was present in two of the 17 cases reviewed by Lange-Cosack. In an infant aged 20 days presented by Kluge, hydranencephaly was associated with meningo-encephalitis of obscure aetiology. Hallervorden and Meyer noted severe maternal trauma during pregnancy in four of the recorded instances, mentioning focal meningeal inflammatory exudate in their own case. The morphological features of our case, 'hydrocephalus', cerebral calcification and macular scarring with pigmentation, also suggest infection, *i.e.*, toxoplasmosis. Although this could not be confirmed, the diagnosis need not be ruled out by the negative skin test (Sabin and Feldman, 1949) or the absence of identifiable organisms in the no-longer active lesions examined at autopsy. The presence of true microgyria indicates a disturbance occurring before the sixth month of gestation (Crome, 1956).

It seems unlikely that the aetiology and pathogenesis of hydranencephaly are identical in all cases. Thus, very similar changes may set in even postnatally, as in the case described by Kopp (1912) where an entire cerebral hemisphere was converted into a hydranencephalic cyst following severe head injury at the age of 3 years. In a case reported by Globus (1921) as porencephaly, but having certain features of hydranencephaly, there was some histological evidence of inflammation and the author suggested that the condition had been caused by an encephalitis originating in intra-uterine life. It has also been suggested that such changes may result from birth injury (Schwartz, 1927), but this opinion was challenged by later workers on the grounds that the condition is often fully developed in newborn and stillborn infants, and that in some other cases, the patients are, unlike cases of birth injury, relatively symptom-free in the immediate post-natal period.

Typical hydranencephaly can be distinguished from the many variants of cystic encephalopathy, in which cavities are smaller and usually multiple, and from porencephaly in which narrow clefts or funnel-shaped defects traverse all or most of the cortex and white matter. However, there is no unanimity in the use of these terms and less typical forms of hydranencephaly are likely to be classified into one of the above groups.

The relation of hydranencephaly to hydrocephalus presents some difficulty. On account of the frequent evidence of preceding cerebral destruction and resorption, hydranencephaly is regarded as an extensive variant of encephaloclastic porencephaly, quite distinct from hydrocephalus, by most of the recent authors (Lange-Cosack, 1944; Peters, 1951; Moser, 1952). On the other hand, raised intracranial pressure, cranial enlargement, and functional obstruction of the cerebrospinal fluid have been frequently observed in hydranencephaly. These have been interpreted as evidence of hydrocephalus developing secondarily as a complication of hydranencephaly.

The problem depends partly on definition. The term 'internal hydrocephalus' usually refers comprehensively to any excessive accumulation of fluid in the ventricular system. The causes are diverse and include obstruction of the cerebrospinal fluid pathway, oversecretion of fluid or failure of its absorption (Russell, 1949). In other cases hydrocephalus may be a part of a complex of developmental abnormalities. It is likely, for example, that parts of the cerebral vesicles which fail to develop offer less resistance to transient rise in intraventricular pressure than the less abnormal ones, and that localized ventricular dilatation, so frequent in cases

of cerebral malformation, may arise in this manner. Ventricles may also dilate passively (hydrocephalus '*ex vacuo*') following atrophy, scarring or resorption of the overlying tissue. If severe and extensive, such destruction may result in hydranencephaly.

Thus, viewed in the light of current definitions, the distinction between hydranencephaly and hydrocephalus would seem to be one of degree, particularly since some of the morphological criteria on which it is largely based have, as stated already, certain limitations.

It may be argued, however, that cases with primary atrophy and destruction of the ventricular wall and periventricular tissue ('encephaloclastic hydrocephalus') should not be included in the general group of hydrocephalus. If so, considerable difficulty will often be encountered in distinguishing between primary and secondary atrophy. The reason for the frequency of raised intra-cranial pressure and of signs associated with it (*vide infra*) in hydranencephaly also remains to be elucidated, although some periventricular and aqueductal stenosis was demonstrated in a few of these cases.

Moreover, some of the less typical variants of hydrocephalus which are common among mental defectives may present certain hydranencephalic features as illustrated by the following two cases.

Case 2. This girl, the younger of two siblings with a family tree free from mental or nervous illness, was born after a normal pregnancy and labour. She failed to develop mentally and was admitted to the Fountain Hospital at 6 months of age. At that time she was characteristically microcephalic with a head circumference of 27 cm. The fontanelles and sutures were closed and the skull showed ridging over the sagittal and lambdoid sutures. The scalp was loose and transversely folded. The only other external abnormalities were two raised vascular naevi, one over the scapula and the other upon the back of the left hand. She had *grand mal* attacks, screamed frequently and failed completely to develop mentally. Routine laboratory tests were negative. During her stay in hospital she had several attacks of respiratory infection, succumbing to one following measles at 16 months.

Necropsy findings, confirmed microscopically, were bronchiolitis, focal collapse and infective atelectasis, and pulmonary oedema.

The brain (Fig. 11), looking like a periwig, was even smaller (116 g. with cerebrospinal fluid) than would be expected from the smallness of the skull (34 cm.) and there was much fluid in the subdural space. The cerebral hemispheres (Fig. 12) above a horizontal plane corresponding approximately to the middle temporal gyri were converted to fluid-filled sacs enclosed by a paper-thin membrane. Conspicuous, somewhat tortuous vessels, coursed over the membrane, the lower half of which was rough on its external surface. The internal lining of the membrane was smooth and glistening. The transition from the upper membranous to the lower solid part of the brain was clear-cut. The latter (Fig. 12) showed microgyria above, and a smooth surface with broad gyri and short, shallow sulci upon its inferior and basal aspects. The anterior commissure was present, the foramina of Monro dilated, the fornices thin and the

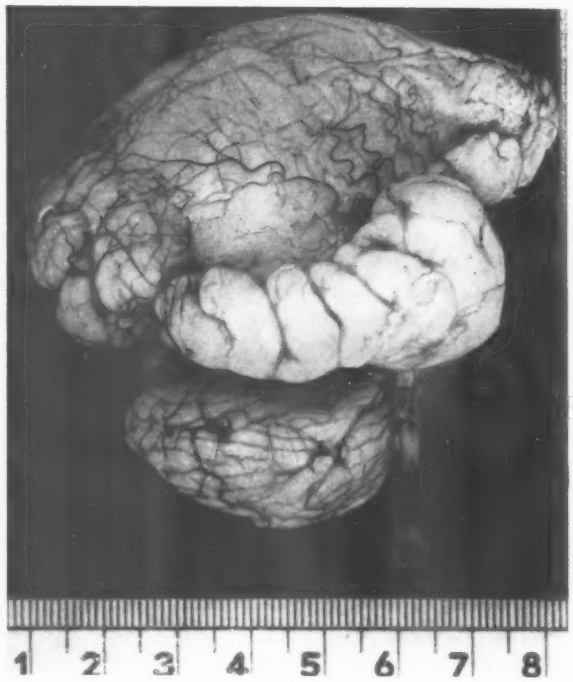


FIG. 11.—Case 2: lateral view of brain with 'periwig' appearance.

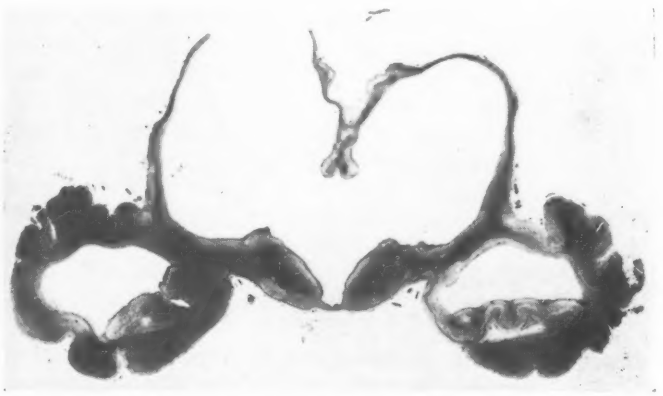


FIG. 12.—Case 2: microgyria and thin cortex in coronal section of entire brain. Heidenhain × 1½.

corpus callosum rudimentary. The choroid plexuses in the lateral ventricles were large. The third and fourth ventricles, with the aqueduct, were dilated. The cerebellum, together with the brain-stem, weighed 42 g. The pyramids were absent, and the inferior olives prominent. The optic and oculomotor nerves were thin. Other cranial nerves and basal blood-vessels seemed normal.

The histological appearances were similar to those in Case 1. The thin membrane was formed by soft meninges and a layer of glial tissue mostly devoid of ependyma. The arachnoid was, however, unlike Case 1, irregularly thickened, fibrosed and deficient in places. There was excessive collagenization and proliferation of blood vessels penetrating the glial layer from the meninges. No recognizable nerve cells or myelin fibres were present in the membrane, which showed focally dense fibrous gliosis and many accumulations of glial cells. Considerable neuronal loss and fibrous gliosis were present in the basal ganglia. Some of the cerebellar folia were thin and poorly cellular, but showed no definite microgyria.

COMMENT. While this case presented obvious hydranencephalic features, there were also significant differences. No history of raised intracranial pressure was suggested clinically or by the morphological findings. In particular the intraventricular pathway was patent. The sharp transition from the inferior solid to the membranous upper part of the brain was striking, and the picture as a whole dominated by pronounced micrencephaly. The findings can be best interpreted as hydrocephalus following uneven pallial agenesis, complicated later by meningeal fibrosis and widespread cerebral gliosis. Morphologically, the condition can be best classified as hydrocephalus with severe micrencephaly.

Case 3. This boy, the first child of a 24-year-old healthy unmarried mother, was born at term by Caesarean section performed for an abnormal lie. The birth weight was 4 kg. Normal milestones were not attained. At 4 months, he began to show signs of hydrocephalus, the head circumference being 46 cm. at 6 months. He was admitted to the Fountain Hospital when 16 months old as a hydrocephalic idiot with spastic quadriplegia and bilateral optic atrophy. The head circumference at that time was 58 cm. and this increased by 1·3 cm. during the next five years. Routine laboratory tests were normal. He failed to advance, developing flexor contractures of the limbs, frequent respiratory infections, and eventually dying at 7 years 3 months of bronchopneumonia—confirmed at necropsy.

Translucent meninges covered an abnormally shaped brain (Figs. 13 and 14), weighing 850 g., in which there was great thinning of the cortex in the occipital region (3-4 mm.) and temporal lobes (0·5 mm.). Below the inferior temporal sulci and extending on to the inferior surface of the lobes the gyral pattern was lost, being preserved elsewhere in the brain. The depth of sulci varied from area to area being greatest in the parietal regions, shallow over the thin temporal or occipital cortex. The sulci were wide and deep in the frontal areas. The cerebellum (with brain stem) weighed 126 g., and showed, bilaterally, around the horizontal fissure

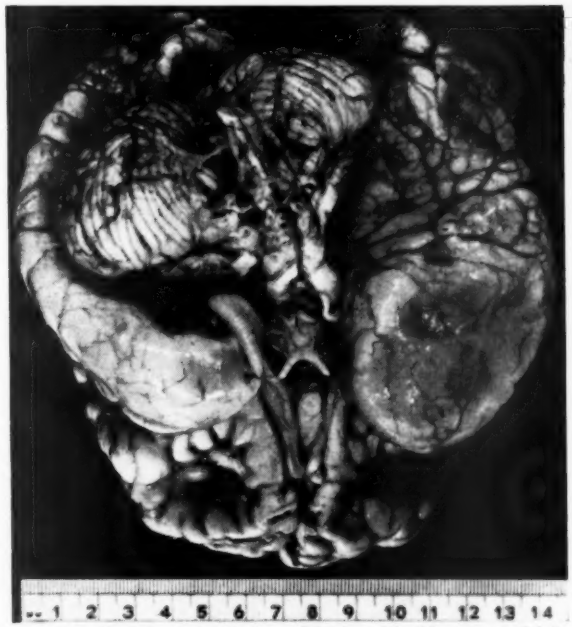


FIG. 13.—Case 3: ventral view of brain with thin temporal lobes.

FIG. 14.—Case 3: extreme thinning of the right temporal lobe and dilatation of the lateral ventricle. The corpus callosum is thin.

several atrophic and yellow discoloured folia. The ventricular system, including the aqueduct of Sylvius (Fig. 15) was greatly dilated. The ventricular lining was

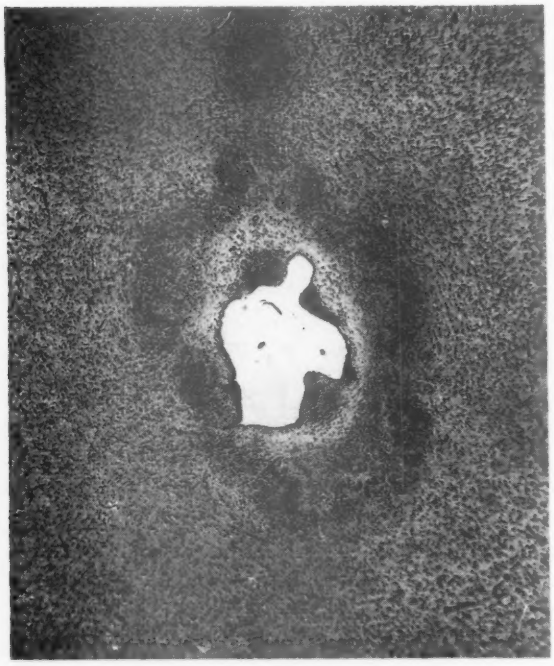


FIG. 15.—Case 3: ependymal granulations and increased gliosis of the aqueduct of Sylvius. Nissl × 25.

smooth except in the fourth ventricle where it had an 'ox-tongue' roughness. The entire corpus callosum was thinned. The pyramids were small. Choroid plexuses and blood vessels appeared normal with the exception of those vessels over the thinned temporal lobes, which were reduced in number and calibre. The optic nerves were small and firm but other cranial nerves appeared normal.

Save for lesser stratification of glial cells and the presence of haemosiderin, the membrane (Fig. 16) representing the thinned temporal cortex was similar to the preceding cases. A few degenerated neurones, some of which were calcified, were present in it. In other areas, laminar structure was preserved even in the thinned occipital cortex. Haemosiderin was present in the cerebellum and adjacent meninges, being most marked in the atrophic folia which showed also loss of Purkinje cells and demyelination. Periventricular gliosis was increased throughout, and in the basal ganglia, the aqueduct, and the fourth ventricle, there were many coarse ependymal granulations. The cortico-spinal tracts were small.

COMMENT. Unlike Case 1, the intraventricular pathway in this instance appeared sufficiently patent. Pronounced ependymal granulations suggest past infection and haemosiderin deposits indicate old haemorrhage. Either or both these factors may have played a significant part in the pathogenesis.

Unlike Cases 1 and 2, there was no evidence of an embryological defect such as microgyria or micrencephaly.

This case is not an uncommon example of communicating hydrocephalus, but the structure of the membrane fulfils the morphological criteria of hydranencephaly (Lange-Cosack).

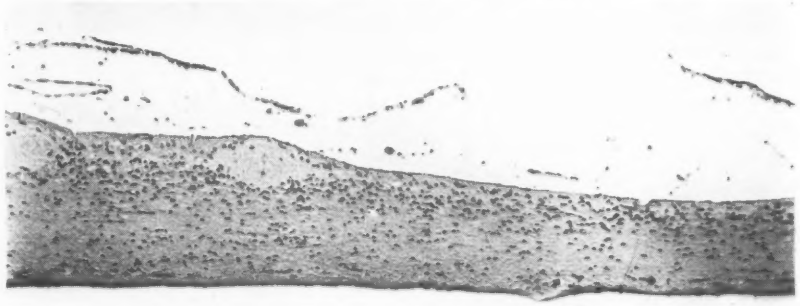
Despite all the unresolved difficulties, it seems useful to retain a special descriptive term for cases with unequivocal features of hydranencephaly, though this is not, perhaps, the happiest designation. Cruveilhier employed it to describe what he believed to be a combination of anencephaly and hydrocephalus, but this is not really the case. Anencephaly is now known to be a distinct and obvious malformation in which the calvarium is not formed and the brain is represented by a disordered hamartomatous arrangement of vascular and immature neural tissue, often described as 'area cerebrovasculosa'. Although a transitional case showing certain features of both hydranencephaly and anencephaly has been described by Hurowitz, it remains unique and seems different from all other instances of hydranencephaly, in which the skull is complete and the brain is not hamartomatous.

It seems preferable, therefore, to avoid the suggestion of anencephaly in the designation, and 'hydrencephaly' is, perhaps, a better term.

Clinical Features

It appears from a perusal of the literature that a few cases of hydranencephaly show cranial enlargement at or soon after birth, and occasional neonatal

FIG. 16.—Case 3: the thin gliosed membrane of the temporal cortex with normal meninges. Haematoxylin and eosin × 50.



jaundice has also been recorded. Usually, however, the newborn is normal in appearance and behaviour for the first days or weeks. Feeding difficulty, frequent screaming and hypothermia are common later, and these are followed by incoordinate eye movements, strabismus and nystagmus. The optic discs are pale; light reflexes may be present or absent. Movements of limbs are usually present and tendon jerks are brisk. In a few weeks or months the head begins to enlarge, intracranial pressure rises and signs of hyper-irritability develop. A 'cracked-pot' sound is often elicited. The pressure of the cerebrospinal fluid is raised and the fluid often shows excess of protein. Spasticity becomes apparent, and many forms of convulsion and tremor occur. The patients are sometimes anaemic. Failure of mental development is increasingly obvious. Transillumination of the skull is a useful and safe diagnostic procedure (Strasburger, 1910; von Bókay, 1923), a reddish reflection being often seen not only over the skull, but through the retinae and ears. The electroencephalogram may be quite flat and the ventriculographic appearances are diagnostic.

Lange-Cosack distinguished two groups of hydranencephaly. Patients in the first, with the greater loss of cerebral tissue and involvement of subcortical centres, are severely disabled and show disturbance of autonomic regulation. They do not survive beyond the first month. The subcortical centres are not involved in the second group, and patients deteriorate less rapidly. It appears, therefore, that the clinical features may enable severe cases to be diagnosed correctly in life. Nevertheless, it is doubtful whether the clinical features are always sufficiently clear-cut to distinguish less severe hydranencephaly from other forms of hydrocephalus. Hydranencephalic patients living long enough to be classed as mentally defective, as our Case 1, could be expected to present even more frequently with atypical features.

Summary

Hydranencephaly is a congenital condition in which the cerebral hemispheres are replaced by thin sacs containing cerebrospinal fluid. Characteristically, the sac wall consists of pia and arachnoid overlying the glial layer—all that remains of the cerebral cortex and white matter.

Hydranencephaly is a descriptive term not implying, on the evidence available, specific aetiology, pathogenesis or clinical features which would always distinguish it from other severe variants of hydrocephalus or porencephaly. It is unfortunate that, etymologically, the term suggests a combination of hydrocephalus and anencephaly, since it is in fact unrelated to anencephaly, hence 'hydrencephaly' is more appropriate.

These conclusions are reached by a review of the literature and the study of a fairly typical case of hydranencephaly in a $4\frac{1}{2}$-year-old epileptic idiot and of two hydrocephalic cases presenting partial features of hydranencephaly.

Toxoplasmosis was suggested by the findings in the first case but this could not be verified.

We are indebted to our colleagues at the Fountain Hospital for access to their case records and their helpful criticism.

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THE WENCKEBACH PHENOMENON AND AURICULAR-VENTRICULAR DISSOCIATION IN CHILDREN

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(RECEIVED FOR PUBLICATION NOVEMBER 26, 1957)

The Wenckebach type of heart block is characterized by a progressive lengthening of the P-R interval until A.V. conduction fails and a beat is dropped. This form of heart block was first described as a clinical entity by Wenckebach (1899) on the basis of radial arteriograms. Since then, this phenomenon has been seen in a variety of conditions including digitalis poisoning, rheumatic fever, tonsillitis and other febrile conditions, diphtheritic and other forms of myocarditis and myocardial infarction. It is not uncommon in adults but few case descriptions refer to children.

Sprague and White (1927), when describing cases of heart block under the age of 30 years, make brief reference to a group of children showing this phenomenon. They described a transient Wenckebach phenomenon in a girl aged 16 years following tonsillectomy and a post-operative cold and more severe grades of heart block in children suffering from diphtheria and rheumatic fever. Zimdahl (1951) and Kuhn, Donoso and Sapin (1954) each described the cases of two children in whom the Wenckebach phenomenon complicated cardiac catheterization. Langen (1956) reported the phenomenon in two 19-year-old youths in whom no cardiac lesion could be found. Ehrentheil, Alimurung and Massell (1952) on analysis of 107 electrocardiograms showed a relationship between sinus arrhythmia and the Wenckebach phenomenon.

A.V. dissociation exists when the auricles and ventricles beat independently. According to Wood (1946) this condition occurs when in nodal rhythm retrograde conduction is completely blocked while forward conduction remains unimpaired. As the rate of discharge from the sinus node is usually slower than that from the A.V. node, the ventricles beat faster than the auricles. Occasionally, however, the auricular rate may be the faster (Magri, 1953).

As in the Wenckebach phenomenon, rheumatic fever, diphtheria, acute febrile states, myocarditis and myocardial infarction may be associated with A.V. dissociation.

This paper presents the case histories of five children with cardiac arrhythmia. Two of these cases are examples of the Wenckebach phenomenon and three cases are examples of A.V. dissociation.

Case Histories

Case 1. A 4-year-old African child was in good health until five days before admission to hospital when she developed an irritating cough. Soon after this, diarrhoea and vomiting commenced associated with anorexia, fever, vague abdominal pains and headache.

Examination revealed a thin undernourished child. Her temperature was 103° F. The pulse rate varied between 50 and 100 beats a minute and was unaffected by respiration. The volume was poor. The heart was not clinically enlarged and no murmurs were audible. The remainder of the clinical examination was essentially negative and the child was investigated as a case of pyrexia of unknown, possibly influenzal, aetiology.

An electrocardiogram recorded 12 hours after admission (Fig. 1a) shows the Wenckebach phenomenon (the first and last complexes) and 2:1 A-V block. This arrhythmia persisted for 96 hours with periods of 2:1 A-V block (Figs. 1b and 1c) and the classical Wenckebach phenomenon (Fig. 1c and 1d).

LABORATORY INVESTIGATIONS. The haemoglobin was 15·8 g./100 ml. with a leucocyte count of 9·000/c.mm. (60% neutrophil polymorphs, 6% monocytes, 29% lymphocytes, 5% eosinophils). The sedimentation rate was 50 mm. per hour (Westergren). The serum sodium was 135 mEq./l. and the serum potassium was 5·7 mEq./l. No pathological organisms were found in the blood, stools or urine. Agglutination tests for typhoid fever and complement fixation tests for viral diseases were negative.

The fever abated 48 hours after admission but the child remained distressed until the fifth day of illness when she improved dramatically. This improvement coincided with a return to normal cardiac rhythm (Fig. 1e).

This patient was observed for a further two months during which period her electrocardiogram continued to show a normal rhythm (Fig. 1f).

Case 2. An African boy, aged 9 years, had been in good health until four days before admission to hospital.

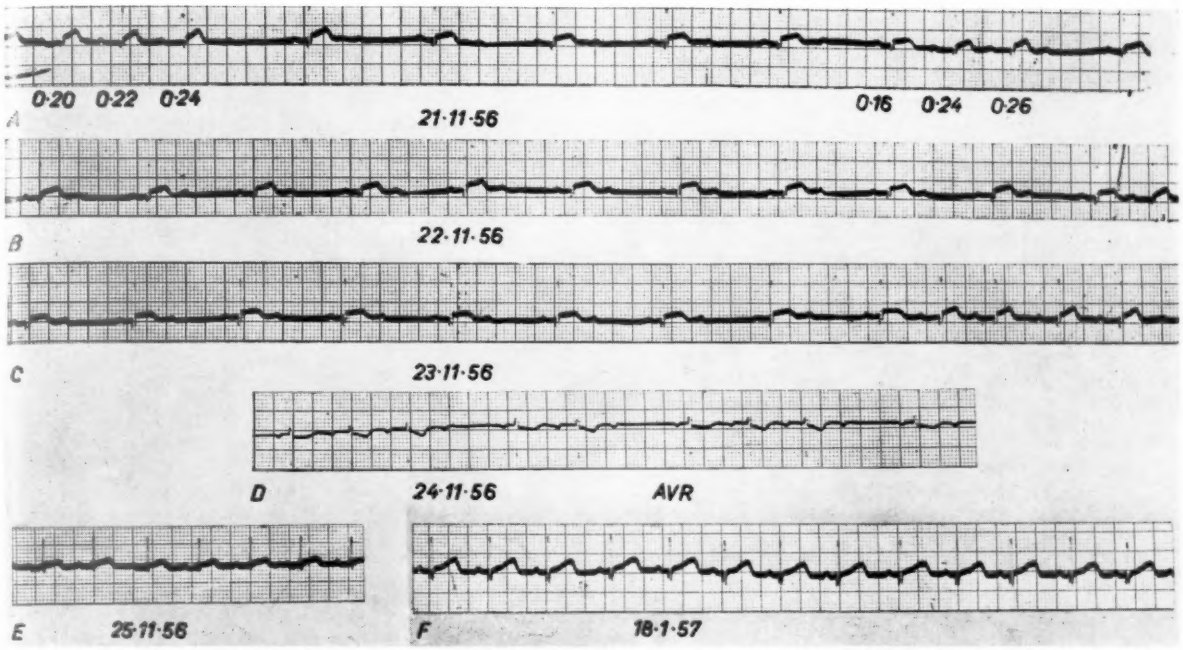

FIG. 1.—Case 1. Pyrexia of unknown, possibly influenzal, origin. Fig. 1a: (standard lead II) classical Wenckebach phenomenon tracing in the first and last three complexes with 2:1 A.V. block which may be considered as extreme form of this phenomenon. Fig. 1b: 24 hours later, a 2:1 A.V. block, which was unaltered the next day (Fig. 1c). Fig. 1d: (lead AVR) a day later, classical Wenckebach phenomenon tracing. Figs. 1e and 1f: normal tracings four days and two months after initial tracing.

He then developed pain in the chest accompanied by a severe cough productive of green mucoid sputum. He had also noticed increasing breathlessness and swelling of the feet.

Examination revealed a dyspnoeic child with dependent oedema to the level of the sacrum. The pulse rate was 120 beats a minute and the volume was full. The blood pressure was 100/75 mm. Hg. The maximum cardiac impulse was located in the 6th intercostal space over the anterior axillary line and suggested left ventricular hypertrophy. A grade III systolic murmur was heard at the mitral area replacing the first heart sound and was conducted into the axilla. The pulmonary second sound was slightly accentuated and clearly split. Crepitations were audible at the bases of both lungs. The liver was palpable 4 fingerbreadths below the costal margin.

LABORATORY INVESTIGATIONS. The haemoglobin was 15·3 g./100 ml. with a leucocyte count of 7,800 per c,mm. (41% neutrophil polymorphs, 4% monocytes, 55% lymphocytes). The E.S.R. was 8 mm. per hour (Westergren), the antistreptolysin titre was 1/200 units and the C reactive protein was ++++. The diagnosis was acute rheumatic carditis with congestive cardiac failure.

During the first 12 hours the child received 1·0 mg. of digoxin orally divided into three doses given 4-hourly. During the next 12 hours he was given three doses of 0·125 mg. and thereafter was maintained on 0·125 mg. twice daily. In addition he was given a low salt diet and received a mercurial diuretic by intramuscular injection on alternate days. On this therapy his pulse rate slowed from 120 to 96 beats a minute. A month later he complained of nausea and vomiting and dropped beats were noticed. Digoxin was discontinued and potassium chloride g. 3 daily was given by mouth. Three days later when cardiac failure was again apparent, digoxin therapy was recommenced without recurrence of the arrhythmia.

Electrocardiographic studies concomitant with the onset of nausea and vomiting (Fig. 2a) showed P-R intervals of 0·28 seconds with occasional dropped beats. The dropped beats occurred at random without lengthening of the preceding P-R intervals. The P-R intervals following a dropped beat were shortened to 0·24 seconds while the electrocardiograms recorded 24 and 72 hours later (Figs. 2b and 2c) showed that the P-R intervals varied in length from 0·28 to 0·32 seconds before a dropped beat occurred.

A return to normal rhythm was recorded four days after the arrhythmia was first noted (Fig. 2d).

Case 3. A 9-year-old African boy had suffered, since the age of 6 years from repeated attacks of pain in the chest, back and feet with periodic swelling around the ankles. His exercise tolerance remained good until four weeks before admission to hospital, when breathlessness occurred on exertion. His symptoms gradually increased until he was immobilized by dyspnoea and a generalized swelling of his whole body.

On examination the child was dyspnoeic with dependent oedema to the level of the sacrum. The jugular veins

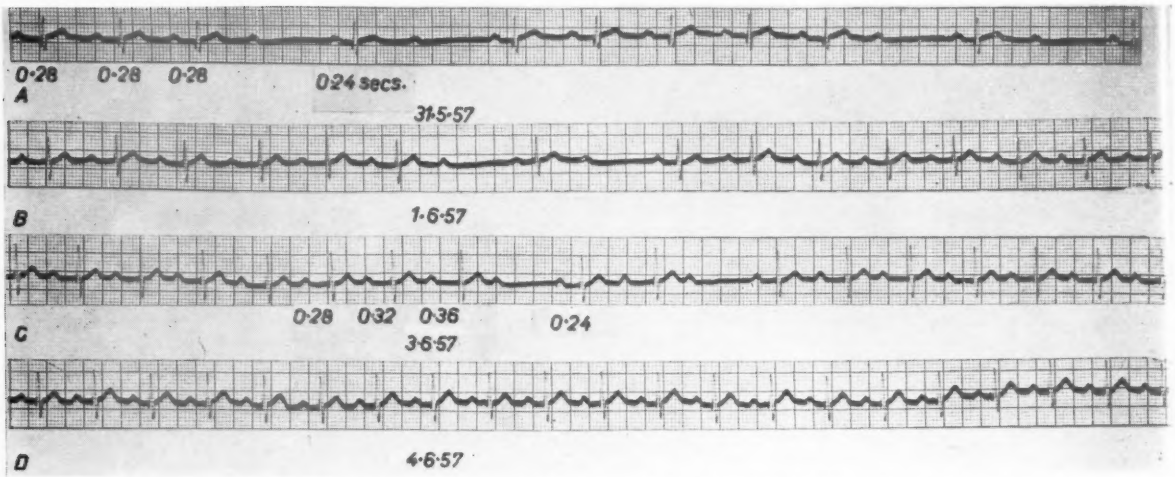

FIG. 2.—Case 2.—Rheumatic carditis on digoxin therapy. All tracings are from standard lead II. Fig. 2a: Mobitz block, constant P-R interval of 0·28 seconds going into a 2:1 A.V. block. P-R intervals following dropped beats are shortened to 0·24 sec. Fig. 2band c: slight variations in P-R interval 0·25-0·32 sec. before dropped beat, i.e. form of varying Wenckebach phenomenon. P-R intervals following dropped beats are shortened to 0·24 sec. Fig. 2d: normal tracing four days after initial tracing.

were engorged to 2 in. above the sternal angle and the liver was enlarged to three fingerbreadths below the costal margin. The maximum cardiac impulse was located in the 6th intercostal space in the anterior axillary line and was characteristic of left ventricular hypertrophy. A grade III systolic murmur, completely replacing the first heart sound was heard at the mitral area and a blowing diastolic murmur radiating from the base of the heart down the left sternal border was also present. The pulmonary second sound was accentuated and split. All the pulses were palpable, regular in rate and collapsing in quality. The left side of the chest was dull to percussion and there was bronchial breathing over the apex of the left lung.

LABORATORY INVESTIGATIONS. The haemoglobin was 11·5 g. per 100 ml. and the E.S.R. was 49 mm. in one hour (Westergren). The C reactive protein was ++++. Urine analysis was negative. A radiological examination of the chest showed cardiac enlargement and consolidation of the whole of the left lung. An electrocardiogram demonstrated bifid P waves of left auricular enlargement. The diagnosis was left lobar pneumonia and congestive cardiac failure with established aortic and mitral incompetence.

He received 0·5 mg. of digoxin orally followed by three 8-hourly doses of 0·25 mg. and a maintenance dose of 0·25 mg. daily. In addition he received 1 ml. of a mercurial diuretic on alternate days. As improvement was slow, the maintenance dose of digoxin was doubled to 0·25 mg. twice daily. Some 28 days later he complained of abdominal pain and vomited. His pulse was found to be irregular and an electrocardiogram (Fig. 3a) revealed a rate of 75 to 100 cycles a minute with well marked sinus arrhythmia. The P waves occurred at regular intervals but bore no relationship to the QRS complexes, showing A-V dissociation.

This dissociation could be temporarily abolished by injecting 0·25 g. of potassium chloride intravenously as is demonstrated in Figs. 3b and 3c which represent the beginning and end of a continuous tracing. A further 0·25 g. of potassium chloride given intravenously produced nodal rhythm (Fig. 3d), which reverted 10 minutes later to A-V dissociation. Fig. 3e taken 18 hours later, and Fig. 3f taken three days later, show a normal tracing with a constant P-R interval of 0·14 seconds.

Case 4. An African child aged 8 years complained of a severe cough, high fever, a stabbing pain in the chest and dyspnoea at rest which commenced 24 hours before admission to hospital.

He was orthopnoeic and the respiratory excursions were obviously limited by pain. The right side of his chest moved poorly on respiration and was dull to percussion. Crepitations, bronchial breathing and diminished air entry were heard over the right base and midzone. The pulse was irregular due to sinus arrhythmia. The heart was not clinically enlarged and a grade II systolic murmur was heard at the mitral area. A diagnosis of right lobar pneumonia was made.

He was treated with 6-hourly intramuscular injections of 500,000 units of penicillin. Two days later the temperature fell to 98° F. and the pulse rate from 120 to 80 beats a minute. Four days after admission the child was still distressed despite the resolution of the infection. An electrocardiogram at this stage shows a ventricular rate of 60 cycles a minute with A-V dissociation (Figs. 4a, 4b and 4c). The P-P and P-R intervals varied in length, the P waves being periodically lost in the QRS complexes. The next day (Fig. 4d) the rate was 54 cycles a minute with sinus arrhythmia present. The A-V dissociation had however disappeared and this return to normal rhythm coincided with a marked clinical improvement.

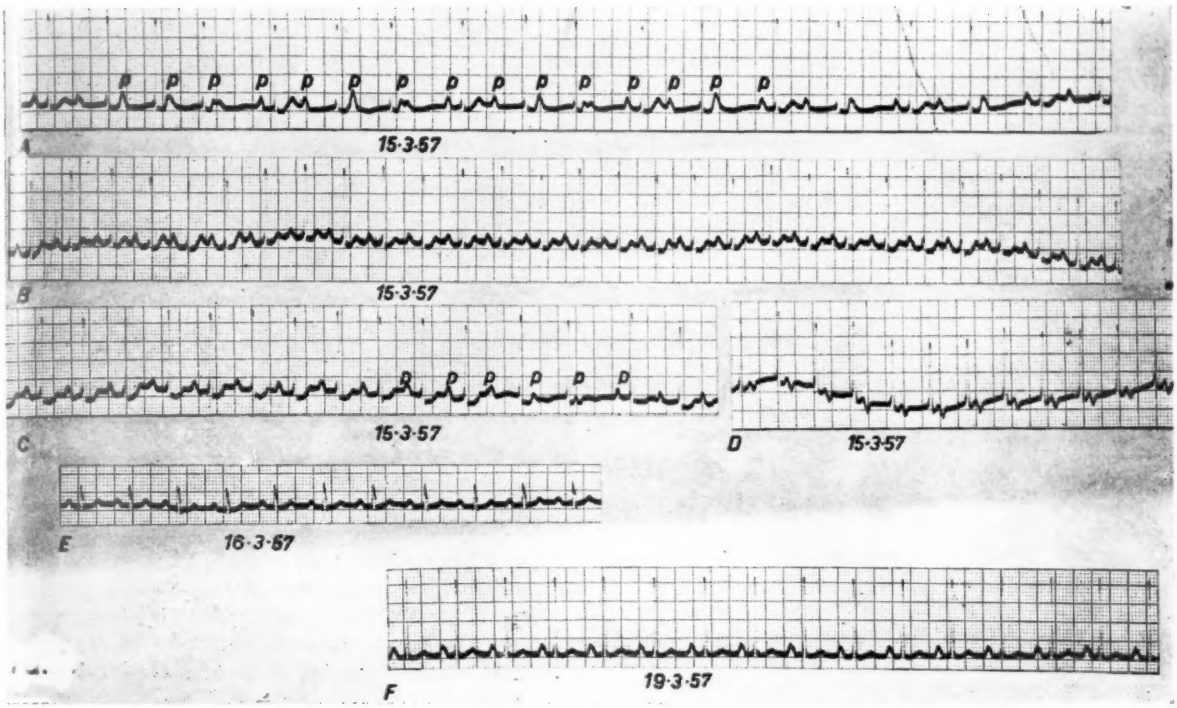

FIG. 3.—Case 3. Rheumatic carditis with left lobar pneumonia. All tracings are from standard lead II. Fig. 3a: constant P-P interval of 0·48 sec. with heart rate of 75 to 100 cycles min. P waves bear no relationship to QRS complexes, showing A.V. dissociation. Fig. 3b and c are beginning and end of continuous tracing during intravenous injection of 0·25 g. of potassium chloride showing tachycardia of 136 cycles/min. with abolition of A.V. dissociation which recurs five min. later (Fig. 3c). Fig. 3d: tracing during intravenous injection of further 0·25 g. of potassium chloride showing that nodal rhythm has replaced A.V. dissociation. Fig. 3e and f: normal tracings 18 hours and two months later.

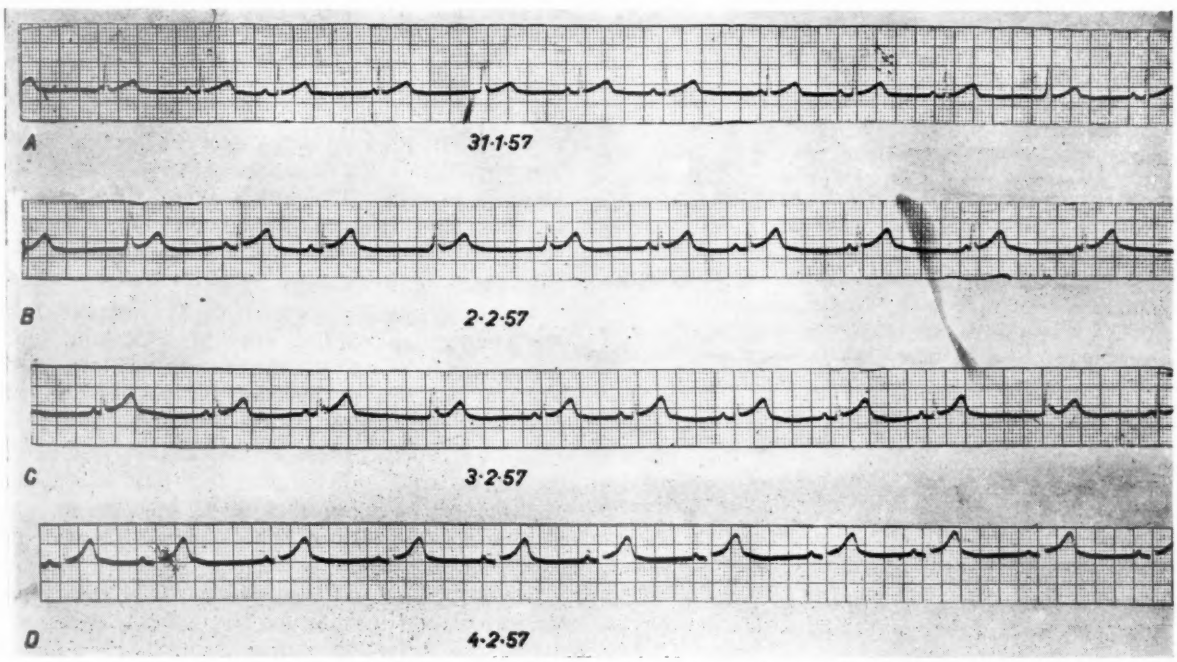

FIG. 4.—Case 4. Lobar pneumonia. All tracings are from standard lead II. Figs. 4a, b and c: sinus arrhythmia with ventricular rate of 70 to 75 cycles/min. P-P intervals vary in length and P waves are periodically lost in QRS complexes. This is tracing of A.V. dissociation. Fig. 4d is tracing taken next day and shows disappearance of A.V. dissociation.

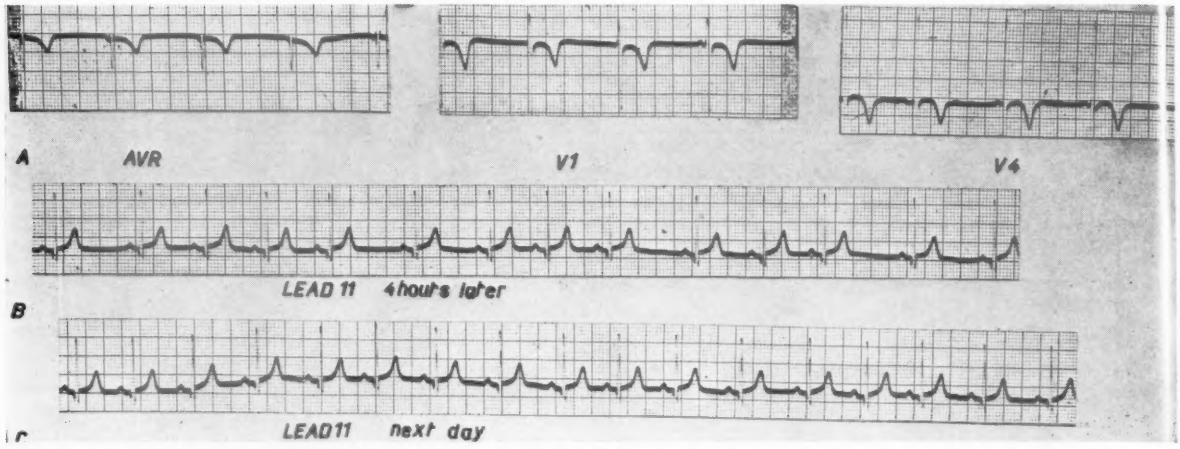

FIG. 5.—Case 5. Belladonna poisoning. Fig. 5a: leads AVR, VI and V4 show A.V. dissociation with P waves moving in and out of QRS complexes. Fig. 5b: standard lead II, taken four hours after preceding tracing and shows A.V. dissociation replaced by sinus arrhythmia. Fig. 5c: standard lead II, normal tracing taken next day.

Case 5. An African staff nurse related the following story about her son aged 8 years.

He had been perfectly well until the night before admission to hospital when he awakened in a state of extreme mental excitement and confusion. His mother found him dashing around his room terrified of the snakes and trains which he claimed were rushing at him. She noticed that he was flushed, his pupils were dilated and his mouth was dry. He had to be strapped down for the night and a doctor called to see him the next day, gave him an intramuscular injection of 'somnifane'. He slept for about three hours and awoke still confused. It was ascertained that he had not had access to drugs but that he might have eaten some berries when playing in the fields.

On examination he was restless, exhibiting quick nervous movements. His skin was hot and flushed, his pupils were widely dilated and reacted to light. His mouth was dry and he was hallucinated. His reflexes were brisk. Clinical examination of the heart revealed no abnormalities and a diagnosis of belladonna poisoning was made.

An electrocardiogram taken because of his irregular pulse is shown in Fig. 5. In the first tracings leads A.V.R., V1 and V4 are shown as they are the only available records. In these leads the P waves can be seen moving in and out of the QRS complexes showing A-V dissociation. A tracing taken four hours later (Fig. 5b) showed well-marked sinus arrhythmia, while the tracing taken on the following day (Fig. 5c) was normal.

Discussion

In childhood arrhythmias occur most commonly with rheumatic heart disease and in patients maintained on high doses of digitalis. In this series arrhythmias were observed in two cases during digitalis therapy given for cardiac failure following rheumatic carditis, in two cases they were associated with acute infections, while the fifth case was associated with belladonna poisoning.

There are very few case reports (Blumgart and Gargill, 1930) of children who showed transitions from A.V. dissociation to sinus arrhythmia. This sequence is shown in Case 5 (Figs. 5a-c), and was associated with belladonna poisoning.

Blumgart and Gargill (1930) demonstrated a distinct relationship between sinus arrhythmia and A-V dissociation. They showed that when the P-P interval lengthens, shortening of the P-R time results. Extreme prolongation of the P-R interval results in a ventricular escape which may manifest itself as A-V dissociation. In this condition the ventricular rate is usually faster than the auricular rate and the P waves fall progressively closer to and are finally lost in the QRS complexes. When the P-R intervals become sufficiently prolonged, a conducted impulse from the auricles may occur, namely, ventricular capture, before A-V dissociation may once again be established.

Many theories have ben advanced to explain these disturbances in cardiac rhythm. Organic interruption of A-V conduction (Mobitz, 1923) has been blamed, as well as exaggerated susceptibility to fatigue of the conducting system (Ehrentheil *et al.*, 1952), and disturbances in conduction just before the A.V. node. Whatever the mechanism, the disturbances in the present series of cases were all of a temporary nature and disappeared when the primary disease was treated.

In the two cases of acute infection and the case of belladonna poisoning which responded to treatment, the heart returned to normal rhythm within one to four days after the primary disease had abated. These children subsequently remained well and

active. Where the primary disease caused marked cardiac damage as in the two cases of rheumatic fever, the patients remained ill with a poor exercise tolerance. The prognosis in these cases depended upon the primary disease rather than the changes in cardiac rhythm. It was, however, observed that all five cases remained distressed during the periods of arrhythmia despite improvement of the primary condition. Clinical improvement coincided with the disappearance of the abnormal rhythm. It is therefore felt that the presence of such electrocardiographic abnormalities suggests the need for strict bed rest while dealing with the primary disease.

A lesson learnt from these cases is that any child suffering from an acute infection who does not make a good clinical recovery when the infection has abated, warrants an electrocardiographic study.

An attempt was made in Case 3 to abolish or modify the arrhythmia by the intravenous use of potassium chloride. This case and that of belladonna poisoning were the only two which reverted to normal rhythm within the short space of 18 hours.

Summary

The case histories and electrocardiograms of five children showing disturbances in cardiac rhythm are described. Three children showed A-V dissociation and two demonstrated the Wenckebach phenomenon.

Case descriptions of cardiac arrhythmias in children are rare. Those records appearing in the literature are associated with rheumatic fever, digitalis poisoning and diphtheria.

The prognosis in these cases is related to the primary condition rather than to the electrocardiographic findings.

The suggestion is put forward that cardiac arrhythmias in children should be treated by careful nursing and bed rest.

My thanks are due to Dr. I. Frack, the superintendent of Baragwanath Hospital for permission to publish these case records and to Dr. E. Kahn and Dr. S. Wayburne in whose wards these cases were treated. I am indebted to Dr. L. Schamroth for his valuable help and criticism and to Dr. A. Barnett and Dr. J. Theunissen who helped in the investigations of Cases 2 and 3. I am indebted for the photographs of the electrocardiograms to Mr. Schewitz of the Witwatersrand Medical School.

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A SALT WASTING SYNDROME IN INFANCY

BY

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(RECEIVED FOR PUBLICATION OCTOBER 14, 1957)

A continued loss of sodium and chloride is a well-known phenomenon which occurs during the course of uncontrolled adrenal insufficiency. Such losses are of serious consequence and in children lead to a failure of growth and development, to asthenia and infection. It is well recognized that many of the symptoms of adrenal insufficiency are due to the disturbance in mineral metabolism, and it is not surprising, therefore, that other conditions where excessive amounts of salt are lost from the body occasionally give rise to a picture that resembles, in many respects, adrenal insufficiency. In passing, we can mention fibrocystic disease of the pancreas, hydrocephalus with arachno-ureteric drainage, patients with heart disease who are hypersensitive to mercurial diuretics, cerebral salt wasting, pink disease and salt losing nephritis where there is advanced destruction of the renal parenchyma and tubular resistance to salt-retaining steroids.

This communication considers a case which does not seem to fit into any of the categories in the above list. It is that of an infant, studied over a five-month period, who demonstrated a renal salt wasting condition in the face of otherwise normal kidneys and normal adrenal function and acid-base balance. It will be shown that this salt wasting defect was resistant to desoxycorticosterone acetate and we suggest that the defect may be due to a refractory state on the part of the tubules to endogenous salt-active steroids or mineralo-corticoids.

Methods

Sodium and potassium concentrations for serum, sweat and urine were determined on a direct reading flame photometer (Domingo and Klyne, 1949), or by a direct reading E.E.L. flame photometer. Chloride determinations, serum *p*H, carbon dioxide content, total body water, total body chloride, were all measured by methods set out in a previous communication (Cheek, 1957). To determine total chloride the volume of distribution of bromide was measured and a micro diffusion method was used as described previously (Cheek and West, 1955). Here the diffusion units of Öbrink (1955) were used (obtained from Rudolf Grave Company, Stockholm, Sweden). These units obviate the need for fixative and for subsequent prolonged washings of the units and increase the accuracy of the method. The variation between duplicate determinations of serum bromide was less than 1%. Before the calculation of the extracellular volume index from the bromide space, 10% of the injected bromide was deducted from the total injected, to allow for the entrance of 8% of injected bromide into the red blood cells and for the fact that the volume of distribution of bromide is 1-2% greater than the chloride space. This correction has been applied previously (Cheek, 1954). Recent work indicates that in the rat almost all the intracellular chloride of the body is in red cells; hence it may be that the corrected Cl or Br space in man is a good approximation to true extracellular volume.

Sweat was collected following a pharmacological stimulus similar to a method described (Mauer and West, 1956). Urinary 17-ketosteroid excretion, and corticosteroid excretion were assayed by accepted procedures (Medical Research Council Committee on Clinical Endocrinology, 1951; Reddy, 1954). To assess urea clearance, urine was collected over a 24-hour period according to the technique described by Landis, Elsom, Bott and Shiels (1935).

Case Report

F.C., a male infant, aged 3 months, was the first-born of parents who had been previously in good health. The mother was admitted to the maternity hospital during the last two months of pregnancy because of an excessive gain in weight, hypertension and albuminuria. Labour was induced and the baby was born two weeks prematurely, weighing 5½ lb. Labour was not difficult and delivery was uneventful. The infant was breast fed for two and a half months but failed to gain satisfactorily. A dried milk mixture was tried temporarily but at the age of 3 months he was brought to the Royal Children's Hospital because of poor feeding, unsatisfactory weight gain and cyanotic attacks. The cyanotic attacks had been noticed during the previous month, and were not associated with feeding. They were not accompanied

by sweating or change in respiration but did seem to occur on hot summer days. The infant's weight at 1 month of age was 6 lb. 11 oz., at 2 months, 7 lb. 11 oz. and on admission at 3 months, 8 lb. 2 oz.

Course in Hospital. It was found that the infant took his feeds poorly and that he preferred milk to glucose water. During the first three weeks routine investigations were carried out, and the weight of the infant fell progressively. It became clear that the baby did not maintain satisfactory hydration. The haemoglobin was 11 g. per 100 ml. The following investigations revealed no abnormality: subdural taps; lumbar puncture; radiographs of the skull and chest; examination of the urine including microscopic examinations of centrifuged deposits; and a Mantoux test. The blood urea was normal, but once, at a time when the child was poorly hydrated, a level of 67 mg. % was recorded. However, radiographs of the kidneys and intravenous pyelography demonstrated normal findings and a subsequent urea clearance test showed that the infant had normal renal function. Restriction of fluid on more than one occasion produced a urine of 1,020 specific gravity which suggested a satisfactory concentrating ability. A urine chromatogram revealed no abnormal amino acid excretion. No evidence of a congenital heart lesion was found.

On the twenty-second day following admission and at a time when hydration was unsatisfactory, serum electrolyte concentrations were determined (Table 1). Next day the fluid intake was increased by giving 5% glucose solution by gavage, and on the 24th day the infant had a grand mal convulsion and continued to appear dehydrated and cyanosed with sunken eyes and poor skin turgor. The serum sodium and chloride concentrations dropped to low levels (Na 124 mEq/l. and Cl 75 mEq/l.). Intravenous therapy was at once started: a blood transfusion was followed by 400 ml. of isotonic saline and 3 g. of NaCl 24-hourly were added to the feeds. Desoxycorticosterone acetate (DOCA) was given intramuscularly at a dosage of 2 mg. 24-hourly. The response was dramatic, hydration at once improved and body weight increased for the first time. The infant became alert and active and the milk intake rose appreciably.

Two oral glucose tolerance tests showed a flat blood sugar curve but the result of an intravenous test was normal. Radiographs of the adrenal gland showed no calcification and 24-hour urine collections made before steroid therapy contained normal amounts of 17-ketosteroids and corticosteroids. (Adrenal function tests will be discussed presently.) The serum sodium concentration remained near 135 mEq/l. while DOCA and 3 g. of sodium chloride were given 24-hourly (Table 1).

On the 43rd day of study, DOCA was discontinued, but the weight still increased. On the 48th day, salt was stopped and the weight, fluid intake, and serum sodium concentration fell. Dehydration recurred and intravenous saline was again given and 3 g. of salt were again added to the milk. The increase in weight over the next period was not so remarkable. On the 63rd day, DOCA (2 mg.) was recommenced, to see if there would be any increase in the rate of weight gain. There was not, and on the 69th day the steroid was discontinued.

On the 78th day of study, salt was stopped and again the fluid intake, weight and serum sodium concentration fell (130 mEq/l.). Hypotonic dehydration returned. For the next week some special investigations were carried out (see below) and on the 86th day salt was again added to the milk feedings, but in the increased amount of 5 g.

TABLE 1
SERUM ELECTROLYTE CONCENTRATION ACCORDING TO NATURE OF TREATMENT

Day of Study	Na_s (mEq/l)	Cl_s (mEq/l)	K_s (mEq/l)	CO_2 Content	*p*H	Blood Urea (mg. %)	Treatment (per 24 hr.)
22	137	102	5·6			19	Nil
24	124	75	5·0				Increased H_2O intake
30	135	91	5·0			22	NaCl 3 g. DOCA 2 mg.
40	134	102	4·7				NaCl 3 g. DOCA 2 mg.
48	130	105	4·5				Nil
58	136	90	5·9				NaCl 3 g.
72	145	93	6·4				NaCl 3 g.
78	130	97	4·8	24·0	7·36		Nil
87	143	98	5·5	22·4	—		NaCl 5 g.
99	122	96	5·0	19·0	7·40		DOCA 4 mg.
105	138	100	5·5	23·3	7·36	22	NaCl 5 g.
120	142	108	4·2	21·8	—		NaCl 5 g.
127	144	110	5·0	23·0	7·35		NaCl 5 g.
134	150	105	5·1	24·0			Nil

in the 24 hours. Weight increased rapidly by more than 1 lb., hydration was restored and the serum sodium concentration rose to 143 mEq/l. For the next week there was no further increase in weight.

On the 93rd day, salt therapy was replaced by 4 mg. of DOCA 24-hourly. With this treatment weight did not decrease further, but hydration seemed poor as evidenced by the sunken eyes and poor tissue turgor. The infant became lethargic and disinterested in feeding. After six days of steroid therapy his serum sodium concentration had fallen to 122 mEq/l. DOCA was then stopped and replaced by 5 g. of sodium chloride in the milk. Well-being returned and the infant began to thrive again. His serum sodium concentration rose to normal levels.

He was discharged to the Out Patients' Department on the 105th day and examined at weekly intervals. On the 133rd day of study, salt (5 g. 24-hourly) was discontinued but the patient continued to progress satisfactorily (Fig. 1). At 8 months of age he appeared

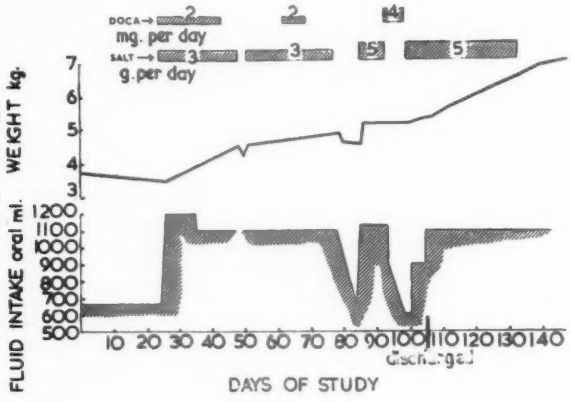

FIG. 1.

normal but undersized. His weight (15¾ lb.) fell on the third percentile of the weight chart.

Special Investigations. In Table 2 the results of investigation of steroid excretion are recorded. Repeated determination of 17-ketosteroid and 11-oxysteroids in the urine demonstrated normal excretion and the response following 25 mg. of ACTH (gel) per day for a three-day period was also normal. The Thorn eosinophil test was performed and disclosed normal function in so far as the eosinophil level dropped progressively from 150 to 11 cells per c.mm. over a three-hour period. On the previous day, two spot counts had revealed 233 and 166 cells per c.mm. These tests with ACTH were carried out during the 78th to 85th day when no therapy was being given. Also during this period, when the weight had reached a low level, determination of electrolyte intake and urine output was made (81st day). The sodium, chloride, and potassium intake was 13·7, 15·8 and 16·5 milliequivalents per day respectively while the urine output contained 12·3, 15·9 and 8·4 milliequivalents for sodium, chloride and potassium. Hence the

TABLE 2

EXCRETION LEVEL OF URINE STEROIDS ACCORDING TO NATURE OF TREATMENT

Day of Study	Corticosteroids (mg. per 24 hr.)	17-Ketosteroids (mg. per 24 hr.)	Treatment (per 24 hr.)
24	2·9	0·18	Nil
52–57 (4-day collection)	1·2	0·19	NaCl 3 g.
82	0·9	0·17	Nil
83–6 (3-day administration)	—	—	ACTH 25 mg.
86	7·7	0·66	NaCl 5 g.

intake and urine output for sodium and chloride closely paralleled one another, and if we consider the expected skin losses for these electrolytes (about 2 milliequivalents per day) the data suggest a negative balance for sodium and chloride. However, balance data derived from such a short period cannot be regarded as very significant.

Data for sweat electrolyte concentrations are set out in Table 3. It can be seen that there was no excessive loss

TABLE 3

SWEAT ELECTROLYTE CONCENTRATIONS ACCORDING TO NATURE OF TREATMENT

Day of Study	Na (mEq/l.)	K (mEq/l.)	Treatment (per 24-hr.)
36	11·4	20·6	DOCA 2 mg. NaCl 3 g.
51	16·4	18·0	Nil
55	11·1	14·4	NaCl 3 g.

of electrolyte from the skin, in fact, the values for sodium and potassium, when the patient was receiving no treatment, are at the lower limit of normal (Cooke, Pratt and Darrow, 1950). When DOCA and/or salt was given the value for sweat sodium was slightly lower.

While the serum sodium concentrations fluctuated with the addition to or subtraction of salt from the food (Table 1)—DOCA exhibiting no sodium retaining effect—the data for serum chloride, carbon dioxide content and hydrogen ion concentration suggest that there was no gross departure from a normal state of acid-base balance.

In Table 4 are recorded the urine sodium and potassium concentrations before and after an intravenous injection (2·5 mg.) of water soluble DOCA. It would seem from these investigations that no appreciable sodium retaining effect was exhibited by the steroid.

In Table 5 data for patient F.C.'s total chloride, extracellular volume and total body water at various stages of treatment are presented. By difference we can record the status of intracellular hydration. For comparison with F.C. we have listed the normal range of values for the corresponding weight of a normal infant, and, for contrast, those of an infant with adrenal hyperplasia and insufficiency and dehydration.

TABLE 4

Na/K RATIO IN URINE BEFORE AND AFTER 2·5 MG. DOCA I.V. (93rd DAY)

Flow (ml./30 min.)	Na(mEq/l.)	K(mEq/l.)
4·8	71	26
4·2	80	26
3·3	90	27
→I.V. DOCA 2·5 mg. 4·0	100	27
5·7	104	27

Patient F.C. had a significantly low total body chloride and calculated extracellular volume while on no treatment (48th day), or following six days of DOCA (4 mg. 24-hourly) (98th day). Total body water was not low in the first instance but normal. Since no weight was lost 4 mg. of DOCA were substituted for salt therapy on the 93rd day, it could be assumed that total water was also normal at that juncture. The data suggest that in both of these periods there was an increase in cell hydration. Three weeks after discharge (127th day) data for total chloride and water and extracellular volume were again obtained. The total chloride and extracellular volume were slightly low but within normal limits.

The infant with adrenal hyperplasia and dehydration showed a reduction of total chloride and extracellular volume. The total water was reduced and the calculated index for intracellular volume also appears low.

From these results it seems that the fluid volume changes in patient F.C. resemble those found in simple sodium loss.

Discussion

The investigations of infant F.C. lead us to the tentative conclusion that there can be in infancy a salt wasting syndrome that is not directly related to the adrenal gland or to gross renal disease. We are aware that, in chronic nephritis with destruction of renal nephrons, a renal tubular salt wasting syndrome can arise which is resistant to DOCA, as Thorn, Koepf and Clinton (1944), have clearly demonstrated. However, the routine methods of revealing disease of renal nephrons carried out in the case of patient F.C. supported the belief that renal function was normal and urine chromatography did not indicate a tubular defect in amino acid metabolism. On the other hand, investigation into adrenal function disclosed no abnormality. The serum potassium concentration was never grossly elevated, nor was there an obvious disturbance in acid-base balance. The sweat concentration in patient F.C. was not elevated as it is in Addison's disease (Conn and Louis, 1950). Such findings suggest that patient F.C. was not deficient in endogenous mineralo-corticoid. The urine steroid excretion before and following ACTH showed a normal pattern of response and the Thorn eosinophil test was also normal. At the completion of this study the patient was normal emotionally and mentally and there was no reason to believe that disease of the central nervous system was present.

In a patient with adrenal insufficiency with salt wasting one might expect that the withdrawal of salt and a high dosage of DOCA (4 mg. 24-hourly)

TABLE 5

TOTAL CHLORIDE AND VOLUME MEASUREMENTS IN INFANT F.C. (SALT-WASTER) COMPARED WITH NORMAL VALUES AND WITH THOSE IN INFANT H.O. WITH ADRENAL INSUFFICIENCY

Infant	Weight (Kg.)	*Total Cl (mEq/l.)	E.C.V.† (ml.)	T.B.W.‡ (ml.)	State of Intracellular Hydration	Treatment (per 24 hr.)
F.C. (salt-waster)	4·5	166	1,240	3,000	+	No NaCl for 24 hr.
Normal	4·5	183-203	1,530-1,710	3,081-3,239		
F.C. (salt-waster)	5·2	172	1,420		?+	After 6 days DOCA (4 mg.)
Normal	5·2	205-225	1,720-1,900			
F.C. (salt-waster)	6·35	272	1,970	4,500		NaCl 5 g.
Normal	6·35	271-291	2,300-2,480	4,340-4,561		
H.O. (Adrenal insufficiency; hyperplasia)	5·6	152	1,370	2,720	—	
Normal	5·6	217-237	1,830-2,010	3,822-4,018		

* For infants of 2-9 Kg., Cl_t = 30·7 weight (Kg.) + 55·0 (SD±10 mEq/l.) (Cheek, 1954).

† E.C.V. = Bromide space corrected for intracellular Br (10%). See p. 252.

‡ T.B.W. = Total body water. Normal values and range derived from data of Friis-Hansen (1957).

would lead to uninterrupted progress. One would not expect deterioration and a fall of serum sodium concentration nor would one expect to find, following such high steroid dosage, a reduction of extracellular volume and loss of total body chloride with a probable increase in cell hydration. Yet these are the changes that took place and, furthermore, intravenous administration of water soluble DOCA did not alter the urine sodium/potassium ratio. It seems reasonable to believe that patient F.C. was not sensitive to DOCA at the level of the renal tubules, and that the therapeutic agent that did guarantee well-being was additional sodium chloride. It is probable that the addition of 3 g. of NaCl was not optimal and that 5 g. per day was more beneficial. Progress in weight and serum sodium concentrations support this belief. Jaudon (1946, 1948) described what he believed to be a fractional insufficiency of the salt and water hormone of the adrenal gland in the early period of life. Asthenia, failure to thrive, cyanosis, failure to maintain hydration, were characteristic of his group of infants. But Jaudon also reported low urinary steroid excretion, hypoglycaemia, a dramatic response to DOCA without salt, and acidosis, none of which were observed in patient F.C.

It would seem from our observations that we may be dealing with renal tubules that are refractory for a time to salt-retaining steroids. The diminished extracellular volume in patient F.C. should have initiated an increased production of aldosterone (Bartter, Liddle, Duncan, Barber and Delea, 1956) which in turn should have enhanced renal tubular reabsorption of sodium. It would seem that this was not the case. Yet the low sweat sodium values suggest an adequate endogenous production of salt-retaining steroids. So we arrive at the suspicion that the renal tubules were sensitive neither to endogenous nor exogenous salt-retaining hormone.

The finding of a flat oral glucose tolerance curve on two occasions while the intravenous curve was normal was of interest. In adrenal insufficiency the gastric absorption of glucose is delayed, but this phenomenon is due to coincidental salt depletion and not to lack of cortical hormone (Althausen, Anderson and Stockholm, 1939; Clark and MacKay, 1942).

While we have been unable to find any similar case reports in the literature, Payne (1954) states that he believes a renal tubular salt wasting condition occurs in infancy and that it is resistant to DOCA. He states that such a condition can threaten for a time the life of an infant but after several weeks spontaneous recovery takes place. The condition was thought not to be related to adrenal insufficiency. It is felt that the present paper supports this contention but further patients and scientific data will be necessary for study before one can accept these findings as representative of a new syndrome. Although the routine renal investigations are normal one cannot be positive that parenchymal disease is not present and is yet to become manifest.

Summary

The case is presented of an infant who failed to thrive and to maintain hydration satisfactorily. He was found to have a renal salt wasting defect. Adrenal and kidney function and acid-base balance were found to be normal. Low sweat electrolyte levels were taken as evidence of adequate production of mineralo-corticoid.

This deleterious clinical situation could be reversed by raising the serum concentration to normal with the addition of 5 g. of sodium chloride to the milk intake. When the patient was off salt or on DOCA only, the serum sodium concentration, the extracellular volume and the total chloride fell or were low and the clinical condition deteriorated. DOCA had no effect on the urinary sodium/potassium ratio.

If electrolyte concentration of sweat is a satisfactory index of endogenous mineralo-corticoid production, then this child's salt wasting condition may be related to a transient disturbance in the response of the renal tubules to this hormone.

We are most grateful to Dr. Robert Southby, the Senior Physician responsible for this patient, for allowing us to undertake these investigations, and to Dr. Ian Robinson for much practical help. Urine steroid determinations were undertaken through the assistance of Miss Anne Moore.

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ANOREXIA AND SEVERE INANITION ASSOCIATED WITH A TUMOUR INVOLVING THE HYPOTHALAMUS

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 4, 1957)

Anorexia in childhood is a common complaint, resulting as a rule from infectious processes, systemic diseases, metabolic disturbances, or, in healthy children, from quantitative or qualitative overfeeding. There are, however, occasional cases in which none of the above-mentioned factors can be held responsible.

The purpose of this paper is to report the case of an infant suffering from obstinate anorexia since birth, which subsequently proved to be related to a hypothalamic lesion.

Case Report

E.B., a 3-months-old female baby of Turkish-Jewish parentage, was admitted to the Paediatric Service of the Bikur Holim Hospital on November 3, 1955. The parents who were not related were in good health, as was an older sister, aged 2½ years. The baby was delivered at full term after an uneventful pregnancy, weighing 3,200 kg. The baby was breast-fed, the feed being supplemented by a cow's milk formula. From birth onwards it had a very poor appetite; it took both the breast and the bottle most unwillingly and in small amounts, and occasionally vomited. Its weight remained practically stationary. The child behaved normally, smiling and taking some interest in its surroundings.

State on Admission. The infant looked emaciated (weight 3,400 kg.), but it smiled readily and followed light. The head was symmetrical and had a circumference of 37 cm. The anterior fontanelle measured $3 \times 2 \cdot 5$ cm. and was somewhat depressed. The visceral organs were without abnormalities, except for a right-sided hernia. The neurological and ocular examinations were negative. Body temperature was normal.

Laboratory Examinations. Analysis of the urine was negative. Results of a blood count were as follows: red blood cells, 4,200,000 (haemoglobin, 10·0 g. per 100 ml.), white blood cells, 8,400 (segmented neutrophils 34%, rod-shaped neutrophils 4%, eosinophils 1%, monocytes 4%, lymphocytes 58%); blood chemistry showed: urea 29 mg. %, sugar 98 mg. %, calcium 9·4 mg. %, NaCl 671 mg. %); total proteins 6·8% (albumin 4·5%, globulin 2·3 %), CO_2 combining power was 52 vol. %; liver function tests were negative. A Mantoux text (1:1,000) was negative. Paper chromatography of the urine showed a normal amino-acid pattern. The stools were of normal colour and consistency; they were negative for parasites and ova. The duodenal juice contained trypsin.

Radiographic examinations of the chest, stomach and duodenum gave negative results.

In view of the child's poor appetite it was fed seven times a day. Yet, throughout its stay in hospital, it fed very poorly and vomited once or twice a day.

There were, however, a few periods lasting from three to seven days during which there was no vomiting. No appreciable weight gain occurred, the child weighing 3,550 kg. on December 12.

Thirty-nine days after the child's admission (December 12), vertical, horizontal and rotating nystagmus were suddenly noted. As far as could be ascertained, no other abnormalities referrable to the central nervous system were present. On December 24, the fontanelle had become tense, bulging and was enlarged to $5 \cdot 5 \times 5$ cm. The baby's eyes had by then the typical 'setting sun' appearance. A lumbar puncture yielded a transparent fluid which contained 11 leucocytes per c.mm. and had a pressure of 220 mm. A Pandy's test showed sugar 53 mg. %, NaCl 827 mg. %. A pneumoencephalogram performed on December 28 showed that both lateral ventricles were markedly enlarged. The pressure of the cerebrospinal fluid at that date was 330 mm. and the reaction to Pandy's test was ++. The head circumference had increased to 41 cm. and the fronto-occipital diameter was 17 cm. A diagnosis of a communicating hydrocephalus was made and the child was transferred to the neurosurgical department of the Hebrew University-Hadassah Medical School.

On January 23, 1956, Dr. E. Peiser operated on the baby. After resection of the 5th lumbar vertebral arch, an anastomosis between the subarachnoidal space and the peritoneal cavity was performed with a partial removal of the omentum.

Following the operation the head circumference decreased from 41 cm. to 40 cm., and the bulging fontanelle subsided, but the child's general condition remained poor and it continued stubbornly to refuse food.

On January 31, eight days after the operation, the bulging of the fontanelle reappeared, the head circumference increased to 42 cm., the fontanelle measured 7×7 cm. A lumbar puncture yielded little fluid under low pressure. The child's condition rapidly deteriorated, and she died on February 2.

Necropsy (Professor M. Wolman, Department of Pathology, Hebrew University-Hadassah Medical School). At autopsy, evidence of extreme malnutrition, and signs of the above-described operation were noted. The peritoneal cavity contained 180 ml. of chylous fluid.

BRAIN. Externally, the membranes of the lower part of the brain were markedly thickened and gelatinous. The gelatinous part stretched from the sella turcica to the anterior aspect of the pons and continued down to the spinal cord. The arachnoid of the cisterna magna was most markedly thickened and contained greyish patches 2-4 mm. in diameter, and about 1 mm. in thickness. Coronal sections through the brain showed severe internal hydrocephalus, most marked in the lateral ventricles with thinning of the brain cortex to between 2-8 cm. The third ventricle was found filled with a gelatinous mass adherent on all sides to the walls except for its upper part (Fig. 1). The mass was greyish and homogeneous, was not sharply demarcated from the brain tissue of the hypothalamic regions, and was continuous with the meninges. The tumour occupied the middle portion of the third ventricle and did not invade the posterior part and the pineal recess. The fourth ventricle and the Sylvian aqueduct were not enlarged.

MICROSCOPIC STRUCTURE OF THE TUMOUR (Fig. 2). The microscopic structure of the tumour differed in the various areas. In some places it had a net-like appearance with small compact nuclei, spheroidal or oval, often lobulated or twisted, surrounded by eosinophilic cytoplasm (Fig. 3). Delicate dendritic processes, with little arborization, emerged from the cytoplasm of some of these cells and gave the tissue its reticular appearance. Between these processes capillaries and thin collagen bundles were found. The tissue space between the processes did not stain. In phosphotungstic-acid-haemotoxylin-stained sections most processes stained purple.

In other areas the tumour was much more cellular (Fig. 4). The cells had mostly vesicular, fusiform nuclei with rounded ends. Most of the chromatin was situated at the nuclear membrane. The cytoplasm of these cells was scanty and stained lightly with eosin. From both ends of the cytoplasm emerged long, delicate processes with very little arborization. In some places the tissue appeared loose with few cells and with a polar arrangement of the nuclei which lay parallel to each other. In these areas the amount of blood vessels and collagen was small.

The tumour infiltrated the brain tissue without clear demarcation and in the infiltrated tissue a marked gliotic reaction was present. In the meninges the tumour infiltrated the proliferated connective tissue of the leptomeninges.

The two main types of cells in this tumour could be identified as piloid astrocytes and oligodendrocytes; accordingly the tumour was considered to be a mixed astrocytoma and oligodendroglioma.

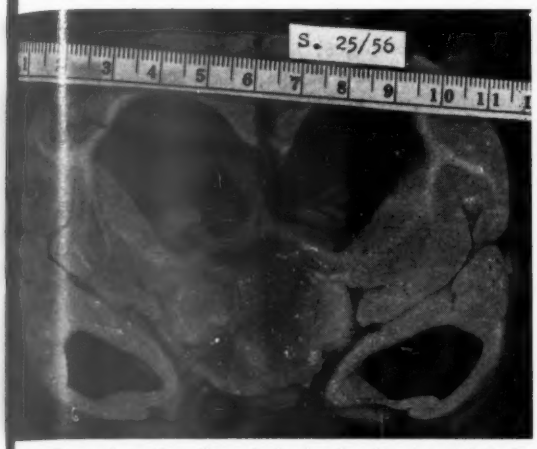
Discussion

The presenting sign of the case reported here was an obstinate anorexia with subsequent lack of weight gain which existed from birth until the child's death at the age of almost 6 months. At the age of 4½ months, signs suggestive of a space-occupying intracranial lesion appeared. At autopsy an astrocytoma, presumably originating in the hypothalamus and extending into and blocking the third ventricle, was found. Since during life and at autopsy no other functional or organic abnormalities were detected, a causal relationship between the hypothalamic lesion and the anorexia had to be assumed.

The role of central nervous centres in the pathogenesis of emaciation has been acknowledged for some time. Gull (1874) described a syndrome of extreme inanition due to a morbid mental state which he termed anorexia nervosa and which is to date by some attributed to hypothalamic lesions. On clinical grounds, anorexia nervosa can hardly be differentiated from Simmonds' pituitary cachexia. The latter disease entity which commonly arises from adenohypophyseal failure was later found to occur also in patients with an intact pituitary, but with tumours or inflammatory processes in the region of the third ventricle (Richardson, 1939; Glanzmann and Wegelin, 1942). The claim that the same symptomatology may be produced by disturbances in any part of the functional unit pituitary-hypothalamus (Zondek, 1923) therefore seems perfectly justified. It is substantiated by experimental observations to the effect that both hypophysectomy (Paulesco, 1907; Smith, 1927) and hypothalamic lesions (Bailey and Bremer, 1921) may lead to profound cachexia.

Russell (1951, 1957) described a syndrome presenting in infancy or early childhood with severe emaciation despite an initially normal or even enhanced food intake, and accompanied by locomotor hyperactivity, over-alertness or even euphoria, initial growth acceleration, hypotension and hypoglycaemia. Hypothalamic tumours, almost always astrocytomas, were established as the pathological basis of the morbid phenomena. The emaciation was attributed to an abnormal energy expenditure resulting mainly from hyperactivity and hypermetabolism.

The present case resembles the syndrome described by Russell with regard to age, the presenting clinical manifestation, emaciation, and the source and

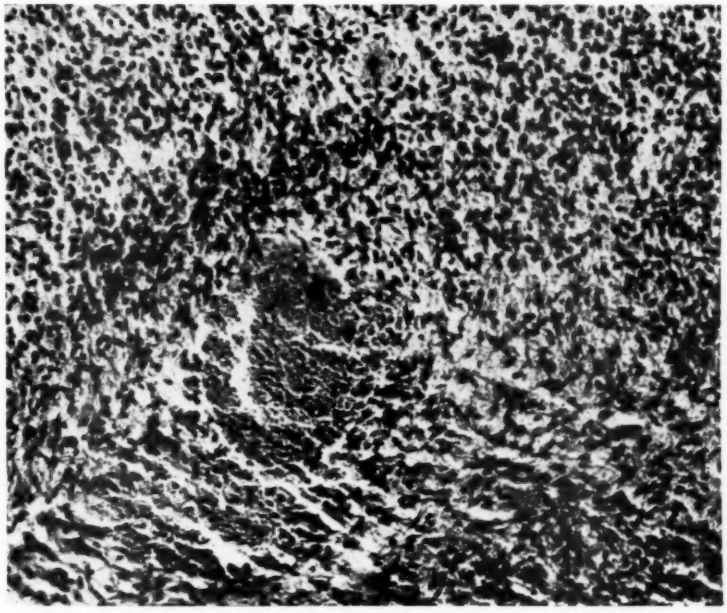


1.—Coronal section through brain showing internal hydrocephalus and tumour mass filling dilated third ventricle.

FIG. 3.—Tumour infiltration of meninges, showing net-like appearance of tumour with spongy areas surrounded by more compact bands. At bottom, surface of medulla. H and E. × 140.

2.—Tumour structure : fibrillary and bipolar astrocytes lying in bundles with many dilated capillaries. H. and E. × 150.

FIG. 4.—A highly cellular area of tumour consisting almost entirely of fibrillary astrocytes.



nature of the underlying pathological lesion. However, it differs from Russell's syndrome by the absence of the accompanying clinical criteria of the lesion and the presence of a very marked anorexia which dominated the symptomatology from the very beginning. Consequently it should be regarded as another variety of the multiple hypothalamic syndromes known to exist.

Hypothalamic obesity has been studied, both clinically and experimentally, much more extensively than hypothalamic emaciation. An essential mechanism of both was recently clarified by Brobeck and his group (Brobeck, Tepperman and Long, 1943; Anand and Brobeck, 1951). Electrolytic lesions in the ventromedial nuclei of the hypothalamus produced in rats and cats voracious hunger and subsequent obesity, whilst bilateral lesions in the extreme lateral portions of the lateral hypothalamus inhibited food intake to the point of starvation. It may be assumed that damage to hypothalamic feeding centres may also upset the delicately balanced regulation of food intake in man. Cases are on record in which the appearance of uncontrollable hunger with associated weight gain or of complete anorexia with associated weight loss could be causally related to hypothalamic lesions (Heaney, Eliel, Joel and Stout, 1954; Zondek and Leszynsky, 1956). Heaney's report concerned a child suffering from lymphatic leukaemia who suddenly developed voracious hunger and gained 4 kg. in 20 days. Necropsy revealed a leukaemic infiltrate in the hypothalamus. This case may well be regarded as the counterpart of our present one and both as clinical reflections of Brobeck's animal experiments.

Regardless of these theoretical considerations we may conclude that hypothalamic tumours should be suspected in infants and young childen in whom a thorough clinical investigation fails to account for a failure to gain weight, or for the onset of sudden weight loss, with or without accompanying anorexia. As Russell pointed out, a long time may elapse before the growing tumour produces signs of increased intracranial tension or other neurological signs. In the present case the cerebral nature of the disease process was unfortunately not suspected until the tumour had obstructed the third ventricle.

From a perusal of the literature it appears that this patient is the youngest patient with an astrocytoma on record. The youngest patient recorded in a series studied by Zuelch (1956) was 4 years old when the first symptoms appeared, while Russell's youngest patients were 3 months of age. In the present case complete lack of appetite with resulting failure to gain weight was evident from birth, and it may be concluded that the astrocytoma was of a congenital nature.

Summary

The case is reported of an infant who suffered from birth from severe anorexia with subsequent failure to gain weight. At the age of 4½ months signs referable to an internal hydrocephalus appeared, which were only temporarily relieved by drainage of the subarachnoidal space into the peritoneal cavity. About a month later the child died. Autopsy revealed an astrocytoma originating in the hypothalamus and extending into and finally blocking the third ventricle.

In view of the persistence of anorexia since birth and the absence of any other cause either during life or at autopsy it is postulated that the astrocytoma was congenital in nature.

I wish to thank Professor H. Zondek and Dr. J. Leszynsky for their advice, and Professor M. Wolman for the pathological-anatomical examination.

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ACUTE SPINAL EPIDURAL ABSCESS: A CASE IN AN INFANT WITH RECOVERY

BY

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(RECEIVED FOR PUBLICATION OCTOBER 26, 1957)

Acute spinal epidural abscess is a neurosurgical emergency in which early diagnosis and prompt treatment are essential if permanent cord damage is to be avoided. For this reason, this uncommon condition has become well-recognized in recent years, and many full accounts have appeared. However, most of the patients described have been adults, and the following case is reported to illustrate the difficulties of diagnosis in a baby before the appearance of neurological signs.

Case Report

P.S. was born on April 11, 1955, and was three weeks overdue. The birth weight was 8 lb. 8 oz. and the delivery was normal. There was some neonatal skin sepsis, presumably staphylococcal in origin. At the age of 11 weeks he was admitted to the Belgrave Hospital for Children with a pyrexial illness, and a disinclination to move the left arm which was held in Erb's position. No other physical signs were found on admission, and he moved the arm normally after 24 hours. The pyrexia later proved to be due to a staphylococcal pneumonia and empyema, and after a desperate illness he recovered completely.

On July 16, 1956, he was again seen at the Belgrave Hospital, the mother complaining that he had seemed unwell for about two days. He had felt hot, and had screamed whenever he was lifted with her hands beneath his armpits or placed on his back. The feeds had been taken well, there had been no vomiting, and the bowels had been open normally. In February and May, 1956, he had two attacks of fever and irritability each lasting about two days.

On admission the temperature was 100·6° F., pulse 120 and respirations 25 per minute. The child was fretful and did not seem to be in any great pain while lying quietly, but he often screamed when picked up. No localized tenderness was detected to account for this. He was teething and the throat was mildly injected. The cardiovascular and respiratory systems were normal. There was no neck stiffness, and there were no abnormal neurological signs. The spleen was slightly enlarged, but apart from this the abdomen was normal.

Laboratory investigations were carried out: W.B.C. was 7,600/c. mm. (neutrophils 40%), film was normal; E.S.R. was 20 mm. in one hour; a patch test and throat swab were negative; radiographs of the spine, chest, pelvis and abdomen were all normal.

The day after admission his condition was unchanged. The next evening his temperature had risen to 103° F. and the respirations had become more rapid. At 3 a.m. on July 19 he began to twitch and appeared about to convulse, and lumbar puncture was performed that morning. The fluid was clear, but the pressure was not recorded as it fluctuated with the child's crying. The fluid showed: W.B.C. 140/c. mm. (91% polymorphs), R.B.C. 30/c. mm., protein 300 mg. %, sugar 83 mg. %. A blood-culture taken at this time later grew *Staphylococcus aureus*.

It was clear that the child was suffering from an infective process, and despite the absence of focal signs it was considered essential to exclude a cerebral abscess. The child was therefore transferred to the Guy's-Maudsley Neurosurgical Unit. On admission there on July 19 he was irritable and crying, and he looked very ill. The temperature was 102·4° F., pulse 134 and respiratory rate 34 per minute. There were no localizing signs of infection and no abnormal neurological signs. He cried when touched or disturbed, but this was not more noticeable when the back was examined. He resented neck flexion, but there was no neck stiffness, and Kernig's sign was not present.

Ventriculography was performed which excluded a cerebral abscess or other space-occupying lesion. Preliminary lumbar puncture gave clear fluid under a pressure of 30 mm., and specimens of cerebrospinal fluid were taken for examination from the right ventricle and from the cerebral subarachnoid space. The results were: lumbar, protein 350 mg. %, W.B.C. 90/c.mm.; right ventricle, protein 55 mg. %, W.B.C. 5/c.mm. As these figures clearly indicated a cerebrospinal fluid block, cisternal puncture was carried out and 2 ml. of Ethiodan (ethyl-*p*-iodophenylundecoate (B.D.H.)) introduced. This was found to be held up largely at the foramen magnum, but it ran in a thin stream down as far as the seventh cervical vertebra, where the obstruction was complete (Fig. 1). To determine the lower limit of the block, a further 2 ml. of Ethiodan were introduced by lumbar puncture. This ran up as far as the fifth thoracic vertebra, at which level there was complete obstruction

(Fig. 2). The appearances were those of an extradural lesion. During the screening procedure the child lay face downward, and he seemed to find this posture particularly uncomfortable. He cried and struggled to turn over.

collection of pus was found. It lay mainly to the lef , and had pushed the dura to the right. Further pus wa found at T1, which proved to be the upper limit. Th laminectomy was continued up to include C7 and C

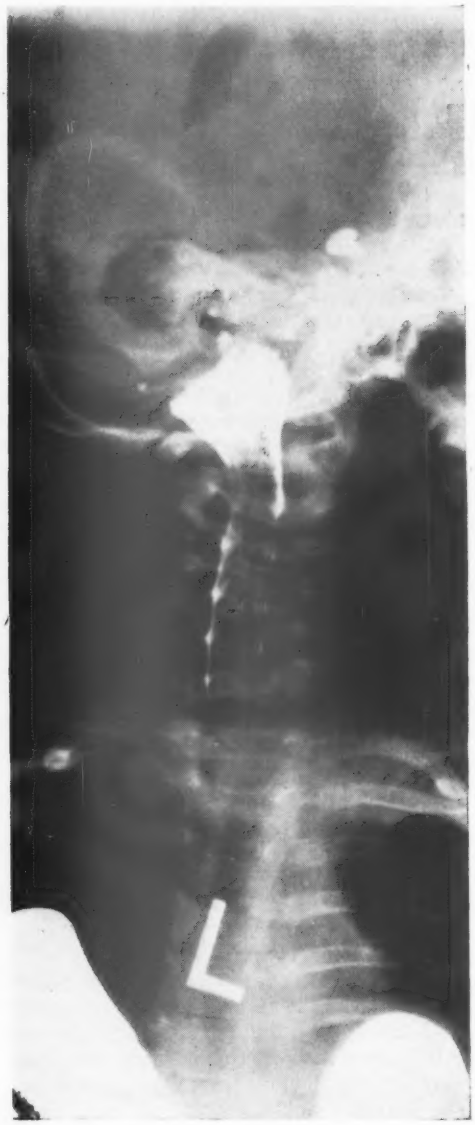

FIG. 1.

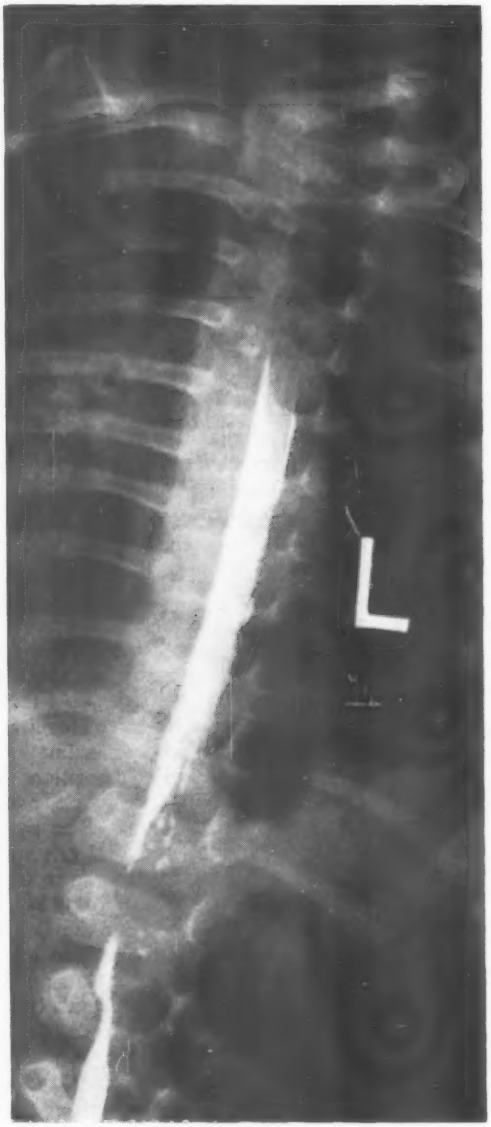

FIG. 2.

Myelographic appearances. In Fig. 1, contrast medium introduced by the cisternal route is seen to be held up for the most part at the foramen magnum, a little running down in a thin stream as far as the seventh cervical vertebra. In Fig. 2, the flow of the lumbar contrast medium is completely blocked at the fifth thoracic vertebra.

A history of repeated staphylococcal infections and the present pyrexial illness suggested epidural abscess as the most likely cause of the block. Laminectomy was therefore performed immediately. The spines and laminae of the third and fourth thoracic vertebrae were removed without any abnormality being encountered, but when the removal was carried up to T2 a large A drainage tube was inserted and the wound closed.

Penicillin and streptomycin had been given before operation, and these antibiotics were continued pending sensitivity tests. The organism was identified as a coagulase-positive staphylococcus which was resistant to penicillin, and this was accordingly changed to terra-

mycin administered systemically, and chloramphenicol instilled locally via the tube.

After some initial anxiety, when the child's temperature rose to 104° F., recovery was rapid and the wound healed perfectly. No neurological signs appeared in the post-operative period, and he began to walk while in hospital. It was thought advisable to continue systemic antibiotic treatment for four weeks, and he was discharged six weeks after the operation. He has remained perfectly well to date (15 months).

Discussion

Infection of the spinal epidural space is always secondary to infection elsewhere in the body, either adjacent or remote. The mode of involvement of the space is obvious enough when the focus is near the involved area, such as an infected rib, but more difficult to understand when spread occurs from some distant site. The metastatic pathway must be either lymphatic or haematogenous, the organism lodging in the epidural tissue and giving rise to an abscess. This child met the staphylococcus very early in life, and it must be presumed that between the repeated episodes it lay dormant somewhere in the body.

Staphylococcus aureus has been the organism responsible for acute spinal epidural abscess in almost all reported cases (Heusner, 1948; Hulme and Dott, 1954). According to Neale (1936) this organism possesses a special affinity for the metastatic invasion of loose fatty areolar tissue of the type which fills the epidural space. The site of the invasion depends upon anatomical considerations. Dandy (1926) pointed out that the spinal epidural space was only present dorsal to the spinal nerve attachments, the dura anteriorly being in contact with the vertebral bodies and their ligaments. In the cervical region the space is only a potential one as far down as the seventh vertebra, but then it begins to deepen and is 0·5-0·75 cm. in depth between the fourth and eighth thoracic vertebrae. It becomes shallow again from the eleventh thoracic to the second lumbar vertebra, and thereafter attains its greatest depth. Consequently an epidural abscess is rarely found above the fourth thoracic vertebra, and is commonest in the lower thoracic and lumbar regions. Dandy considered that local trauma was an important inciting agent in the development of haematogenous infection. An alternative view of the mechanism of invasion of the epidural space was put forward by Browder and Meyers (1937). They considered that haematogenous spread first occurred to a vertebra, the epidural space then being secondarily involved from this focus of infection. No evidence of vertebral involvement was seen in the present case, either in the *x*-rays or at operation, but it could have been so small as to be invisible. Once the abscess is established, the spinal cord is in grave danger. Not only is it subjected to direct compression but the infection may also bring about extensive damage by producing thrombosis of its blood-vessels. In the latter case, the most severe neurological signs may occur very suddenly indeed.

The early symptoms in adults are remarkably uniform. There is a pyrexial illness, localized back pain of the most agonizing intensity, and radicular pain. Familiarity with this picture should make the diagnosis possible before neurological signs appear, but, in a young child with a pyrexial illness and no neurological signs, the condition might well be overlooked if attention is not drawn to the back. Although in this case no local tenderness was found, it was thought in retrospect that significance should be attached to the mother's observations on the type of handling which caused him to scream, and to our own observation of his discomfort when he lay face downwards or was picked up. The features which are of diagnostic importance may then be briefly summarized: (1) A history of infection which may have been weeks or months beforehand. Boharas and Koskoff (1941) found the average interval in 85 cases to be 4·2 weeks, but in one case it was as long as three years. (2) Trauma to the back. (3) An unexplained pyrexial illness. (4) Tenderness of the spine. This may be present on physical examination, or may be suggested by the child's disinclination to lie on its back or face downwards.

If an epidural abscess is suspected, lumbar puncture should be performed with caution, and with frequent removal of the stilette and aspiration as the needle is advanced. Pus in the epidural space may be encountered giving the diagnosis, but if the needle is inadvertently passed through the abscess into the subarachnoid space, then meningitis may result. When the subarachnoid space is tapped, the likely finding is a partial or complete spinal block, with the characteristic manometry and protein elevation. There is a moderate pleocytosis.

There are few reports in the literature of myelography as a diagnostic aid. In adults, although the site of the abscess may be determinable by clinical testing, it seems reasonable to perform this investigation to ascertain its exact level and extent. It should be noted though, that lumbar myelography may prove difficult if a second lumbar puncture has to be done to introduce the contrast medium. The initial diagnostic puncture lowers the pressure of the cerebrospinal fluid, which will already be low if spinal block is present, and when a needle is

introduced for the second time an unsatisfactory flow of the fluid is obtained. In these circumstances the contrast medium is very likely to go between the arachnoid and the dura instead of into the subarachnoid space. It was these considerations that underlay the selection of the cisternal route for introduction. Lumbar myelography then proved to be necessary in addition, and was fortunately successful. In the case of P.S., the apparent block was much longer than the extent of the abscess, which may have been due to an associated arachnoiditis.

The treatment is immediate laminectomy and evacuation of the abscess, a small tube drain being inserted to the site before closing. There is no need to leave the wound open. The appropriate antibiotic should be given systemically and locally. The results are excellent if operation is performed before the onset of neurological signs (Heusner, 1948). Operation is urgently required at this stage, for, as has been pointed out, cord damage may come on with great rapidity. If signs of this have already appeared, then permanent paralysis or death is almost certain.

Summary

The case is described of a 15-month-old baby in whom an acute spinal epidural abscess was successfully treated without residual symptoms. The importance of early diagnosis is emphasized, for, if laminectomy and drainage are performed before the onset of neurological signs, complete recovery is to be expected. Once spinal cord damage has taken place, however, then permanent neurological deficit or death is almost certain. The diagnostic difficulties and pathology of the condition are discussed.

We are indebted for permission to report this case to Dr. Mary Wilmers of the Belgrave Hospital, and to Mr. P. H. Schurr, under whose care the child was admitted to the Guy's-Maudsley Neurosurgical Unit. We would like to thank Mr. Murray A. Falconer, Director of the Unit, for his help and advice in the preparation of this paper, and Dr. R. D. Hoare for assistance with the radiological aspects and for permission to reproduce the myelograms.

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COW'S MILK ALLERGY IN INFANCY

BY

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(RECEIVED FOR PUBLICATION OCTOBER 7, 1957)

It appears that, in this country, allergy to cow's milk, manifesting itself in infancy, is still regarded as a rarity. Borman (1953) describes milk sensitivity in infancy as a rare condition and the only case report in the available British literature is that of Brodribb (1944). The purpose of this paper is to present the clinical findings in one infant in whom the diagnosis of milk allergy appears to have been proved and to summarize the features described in the literature.

Case Report

C.C.L. (No. 29911), a male first infant, whose father had suffered from seasonal allergic rhinitis for several years, was born on January 6, 1957. He was seen on February 2, 1957. After a normal pregnancy he was delivered at full-term, weighing 8 lb 2 oz., and was entirely breast fed up to five days before admission. During this period he had been contented, was feeding well and had apparently gained weight. At this time, his mother decided to change to artificial feeding because her milk supply was diminishing. A half-cream preparation of dried milk was used. Four days later, he became reluctant to take his feeds, vomited frequently and developed a widespread rash. His mother remarked that he looked ill, seemed apathetic and listless, but cried if disturbed or if attempts were made to feed him. His stools, previously formed, now became loose, frequent (six to eight in the previous 24 hours) and were noticed to contain mucus. He was admitted to hospital.

On admission, he weighed 8 lb. 13 oz., and showed clinical evidence of mild dehydration with slightly inelastic skin and rather sunken eyes. His whole body was covered with a bright red rash, erythematous on the trunk and limbs and urticarial on the face and scalp, with a tendency, in places, to ring formation. His palms and soles were a uniform bright scarlet colour. A soft systolic bruit was audible to the left of the sternum but no other abnormal physical signs were detected. He was afebrile and his heart-rate was 132 per minute. During the examination he passed a watery, green stool containing a good deal of mucus.

He was then offered feeds of half-strength Hartmann's solution which he took eagerly without vomiting. When seen again 16 hours later, the rash had completely disappeared and he appeared more contented and well hydrated. A provisional clinical diagnosis of cow's milk allergy was then made.

The results of laboratory investigations were as follows: stool cultures on three successive days were negative for the enteric, dysentery and type-specific *E coli* groups. No pathogenic organisms grew from blood cultures. There was a faint trace of albumin in the urine, but it was free from deposit and on culture was sterile. A radiograph of the chest was clear. A blood count showed haemoglobin, 76%; red blood cells, 3,900,000 per c.mm.; white blood cells, 15,800 per c.mm.; polymorphs, 38%; eosinophils, 18%; lymphocytes, 41%; and monocytes, 3%. W.R. and Kahn tests on maternal blood were negative.

Stained films prepared from the mucus found in his stools showed large numbers of eosinophil cells. A scratch test using cow's milk produced an immediate urticarial weal, 1·5 cm. in diameter.

After 24 hours on clear fluids, he was offered feeds of expressed breast milk obtained from the breast milk bank at St. David's Hospital, Cardiff. These were taken eagerly without vomiting, his stools became normal and during the first few days he gained 8 oz. in weight, and appeared to be a normal contented infant. On February 13, he was again offered the same preparation of half-cream dried milk and, within a few hours, he became extremely reluctant to take a feed, vomited repeatedly and again passed frequent, loose stools. A faint roseolar rash appeared on his trunk and face and his weight fell to 8 lb. 10 oz. Feeds of half-strength Hartmann's solution were again taken quite eagerly.

On February 17 it was decided to restart feeds of expressed breast milk and again, within a few hours, his symptoms had cleared. His subsequent progress was completely satisfactory and on March 7 he weighed 10 lb. 4 oz. It was then decided to try the effect of feeding him with a soya-bean preparation known as Soyolk, composed of:

	%		%
Fat ..	20	Glucose ..	5·7
Protein ..	41	Ash ..	4·8
Carbohydrate ..	18·59	Fibre ..	2
Moisture ..	7	Calcium ..	0·2
		Phosphate ..	0·71

For a few days, these feeds were taken quite well but he gradually began to lose weight, became irritable, vomited occasionally and passed loose, bulky, and offensive stools. On March 14, expressed breast milk feeds were restarted and his weight began to increase

again. On March 31 he weighed 11 lb. 1 oz., on April 24, 12 lb. 4 oz. and on May 19, 13 lb. 5 oz.

On April 2, oral hyposensitization to cow's milk was attempted, starting with one drop daily and doubling the dose each day. On April 9 he was taking 1 dr. daily and, subsequently, the dose was increased by 1 dr. daily. No untoward effects were noted until April 13 when he was taking 5 dr. His stools then became rather loose and the dose was not increased until they were more formed on April 25. No further difficulties were encountered and by May 20 he was taking four-hourly feeds, each of 8 oz. of cow's milk, without any abnormal symptoms or signs (Fig. 1).

He has since progressed quite satisfactorily. On September 6, 1957, he weighed 17 lb., was taking cow's milk, rusks and cereals without difficulty. His stools were well-formed and free of mucus. The cow's milk scratch test now produced an area of erythema slightly less than 1 cm. in diameter.

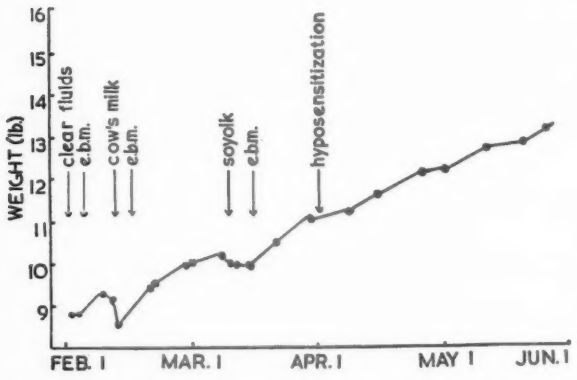

FIG. 1.—Effect of different types of feed on infant C.C.L.'s weight gain.

Discussion

Diagnosis. The findings in the patient described here seem to leave no doubt as to the correct diagnosis. Collins-Williams (1954) states that where a diagnosis of gastro-intestinal allergy is postulated the following criteria must be satisfied: (1) The history must be compatible with the diagnosis of allergy. (2) A specific allergen must be determined. (3) Symptoms must appear within a reasonable time after ingestion of the allergen. (4) Symptoms must disappear within a reasonable time after exclusion of the food from the diet. (5) Symptoms must return when the food is reintroduced. (6) The food must be one commonly tolerated without difficulty by most people. (7) The diagnosis must be supported by other allergic manifestations to the same allergen, e.g., urticaria. (8) The diagnosis is supported by other known allergies in the same patient. (9) Positive findings in other diagnostic procedures such as blood and gastro-intestinal eosinophilia, positive radiological findings, gastric or sigmoidoscopic examination, effects of drugs and results of skin tests would be of confirmatory value.

Most authorities stress that the diagnosis is essentially a clinical one and that skin tests are unreliable.

Clein (1954) reports that, in a series of 206 patients sensitive to cow's milk, there were two or more allergic persons in the same family in 175 cases and one allergic parent in 168 cases. Kane (1957) describing 102 patients found a family history of allergy in 80%.

Incidence. Figures obtained from the literature seem to vary considerably. Clein (1951) states that one in 15 infants are allergic to cow's milk in some degree. Collins-Williams (1956) in a series of 3,000 patients aged from birth to 15 years seen in private paediatric practice, but excluding all those referred with possible allergic symptoms, found an incidence of 0·3%. He also quotes other observers as giving figures varying from less than 0·1% to 7%.

Pathogenesis. Kane (1957) reports that the intestinal tract of a young infant is more permeable to intact protein than that of older children and adults. Collins-Williams (1955) feels that the milk-sensitive infant falls into one of four categories: he may be sensitized to the factor common to both cow and goat lactalbumin or to the species specific factor of cow lactalbumin alone. With either of these categories there may be sensitization to casein as well. Finally, and much less frequently, he may be sensitized to casein alone. This would explain the well-known observation that some cow's-milk sensitive infants fail to improve on a diet of goat's milk.

Brodribb (1944) felt that the allergen appeared to be either lactalbumin or lactoglobulin. As both occur together in the preparation of dried milk the exact identity seemed to be of little practical importance.

Clein (1954) stressed that the symptoms could be explained on the basis of the usual pathological changes occurring in allergy: oedema of mucous membranes, spasm of smooth muscle and excess mucus secretion.

Tudor (1956) states that unless the child is sensitive to the lactalbumin of cow's milk, goat's milk is not a successful substitute because the casein is identical in cow's milk and goat's milk. It seems, therefore, that any of the proteins occurring in cow's milk may act as the allergen.

Glaser (1956) quotes investigations which seem

to confirm that, while human and cow lactalbumin are completely species specific, this is not so in the case of animals as closely related as the cow and goat. However, lactalbumin is markedly heat labile since there is a decrease in antigenic reactivity even at 60° C., which becomes progressively more marked as the temperature is increased. This would explain why evaporated cow's milk, in which the lactalbumin is practically completely denatured by heat is often as satisfactory as goat's milk in the feeding of milk-sensitive infants. Casein, however, is relatively heat stable, no change being noted in its antigenic activity until the temperature reaches 100° C. The changes then taking place probably explain why superheated cow's milk is occasionally tolerated by cow's milk sensitive infants.

Symptoms. The age of onset of symptoms varies with the time of starting cow's milk feeding but Clein (1954) reported that symptoms appeared in 82% during the first four months and in 89% during the first year of life. The symptoms attributed to milk allergy vary widely and are summarized in Table 1.

Investigations. Laboratory and radiological investigations can only be of confirmatory value in the diagnosis which is essentially a clinical one. Frequently, all such tests are found to be within normal limits.

Treatment. The essential treatment is to remove the offending allergen from the infant's diet and to replace it with a food which provides the necessary basic requirements for adequate growth. Glaser (1956) suggests that in some mild cases boiled or evaporated cow's milk may prove satisfactory; goat's milk is also worthy of trial but, in a high proportion of cases, results are disappointing. He regards human milk as ideal but dismisses it as impracticable because of the difficulty and expense involved in obtaining an adequate supply. The same author has found Nutramigen, a hydrolysed casein preparation, disappointing but agrees that other authorities have had considerable success with it. He also states that it is possible to use a food prepared with strained meat as the protein base.

Various foods prepared from the soya bean have been reported for several years as containing all the amino-acids necessary for the normal growth and development of the human infant, but recently it has been suggested that they may be slightly deficient in methionine. In our patient, a trial of Soyolk was made but, because of difficulty in feeding and the passage of loose, bulky stools, it was quickly discontinued. Glaser (1956) reports that such symptoms occur frequently for the first few days and suggests that the preparations should be tried at half strength at the beginning. It is possible that persistence

TABLE 1

PERCENTAGE INCIDENCE OF SYMPTOMS ATTRIBUTED IN THE LITERATURE TO COW'S MILK ALLERGY

Symptoms	Kane (1957) (No. 102)	Clein (1951) (No. 140)	Rosenblum and Rosenblum (1952) (No. unknown)	Clein (1954) (No. 206)
	%	%	%	%
Eczema	74			44
Vomiting and diarrhoea	20		15	
Irritability ; colic	37	29	5	31
Asthma	1			7
Recurrent rhinorrhoea	2			13
Vomiting		39	8·3	
Diarrhoea		24	31·6	22
Mucus in stools		6		
Blood in stools		5		
Anorexia		4		3
Diarrhoea and colic			16	
Diarrhoea, vomiting and colic			20	
Pylorospasm				33
Cough, croup, etc.				17
Constipation				4
Urticaria ; angio oedema				1
Apathy, cyanosis, collapse				2
'Very unhappy all the time'				19

Other clinical features which have been attributed to cow's milk sensitivity include haematemesis, coeliac syndrome, ulcerative colitis, regional enteritis, enuresis, convulsions, headache, migraine and behaviour disturbances.

Bigler (1955) stresses that the picture may vary from a very mild upset to a severe illness and that symptoms may last from a few months up to several years. The infant may become desensitized spontaneously as happens in other forms of allergy.

with this type of feeding might have led to greater success in our patient.

Oral hyposensitization has frequently been reported as being unsatisfactory, but it was a worthwhile and simple procedure in this case.

Conclusions

Abt (1912) mentioned that some infants have an idiosyncrasy to cow's milk which produces 'toxic symptoms and injuries to the baby'. Since then numerous reports have been published on the subject in foreign literautre but, in this country, the condition is still regarded as a rarity. The patient described here appears to be a fairly obvious example of cow's milk sensitivity; there have been reports of even more acute cases such as infants dying of anaphylactic shock. Although it should be accepted that such acute types are by no means common, a more careful search might well lead to the discovery of the relatively minor forms of the disease. The first essential step in diagnosis is elimination of cow's milk from the diet. This would be simplified considerably if a food similar to Nutramigen were easily available in this country.

Summary

An example of sensitivity to cow's milk in an infant is described and the available literature summarized. In this patient, replacement of the cow's milk by human milk and subsequent oral hyposensitization produced satisfactory results.

I am grateful to Dr. P. T. Bray and Dr. D. A. Williams for their help and advice in the preparation of this paper.

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FRANK BERIBERI IN A 4-MONTH-OLD INFANT

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 5, 1957)

Case History

A boy, S.A. 4785/344, aged 4 months, was admitted to the Clinic on February 14, 1957. He was the third child of healthy parents and was born without complications after a normal pregnancy, weighing 4 Kg. The developmental pattern was normal and he never had any illnesses. He was breast-fed till he was 3 months old and he was then given a butter-flour mixture, prepared from overmilled wheat meal. No juices were regularly added, nor any vitamins supplied.

The illness started suddenly with anorexia. The baby was disinclined to feed from the bottle, milk was regurgitated, but not water. He was restless and whining. Constipation, diminished excretion of urine, hoarseness and stiffness of the neck occurred. Two days before admission the child was pale, dyspnoeic, drowsy and had developed diarrhoea.

Upon admission the patient looked acutely and gravely ill. He was cyanosed, there was extreme tachycardia and respirations were 80 to the minute and grunting in character. Nevertheless he was obviously a well-developed and well-nourished child. He weighed 7·1 Kg. and was 67 cm. long. His temperature was normal.

Physical examination revealed rachitic craniotabes, tense and bulging fontanelle, opisthotonos, distension and pulsation of the cervical veins and bilateral loss of the patellar reflexes. There was definite cardiac enlargement in all diameters, with the apical impulse in the left anterior axillary line. Heart sounds were muffled and distant, of poor quality, and the second pulmonic sound was accentuated. A marked gallop rhythm was present. The liver was palpable two fingerbreadths below the right costal border.

Laboratory findings were as follows: Tuberculin skin tests were negative. Wassermann reaction of the blood and cerebrospinal fluid was negative. The erythrocyte sedimentation rate was normal. Examination of the peripheral blood showed haemoglobin 62%, red blood cell count 4·3 million, white blood cell count 10,680, with 35% polymorphonuclears, 3% band forms, 61% lymphocytes and 1% monocytes. The total serum protein was 6·45 g. per 100 ml., albumin 5·41 and globulin 1·04 g. per 100 ml.; serum calcium 9·9 mg. % and phosphate 4·7 mg. %. The cerebrospinal fluid showed a cell count of 4 lymphocytes per c.mm., 20 mg. per 100 ml. total protein and 70 mg. per 100 ml. sugar.

Routine urine analysis was normal. However, testing for phenylpyruvic acid by adding a few drops of 10% ferric chloride solution to the urine acidified with dilute sulphuric acid, produced an intense dark bluish green colour.

A radiograph of the chest showed a generally enlarged cardiac shadow with an enlarged right atrium and with a loss of muscular tone (Fig. 1). The radiographic

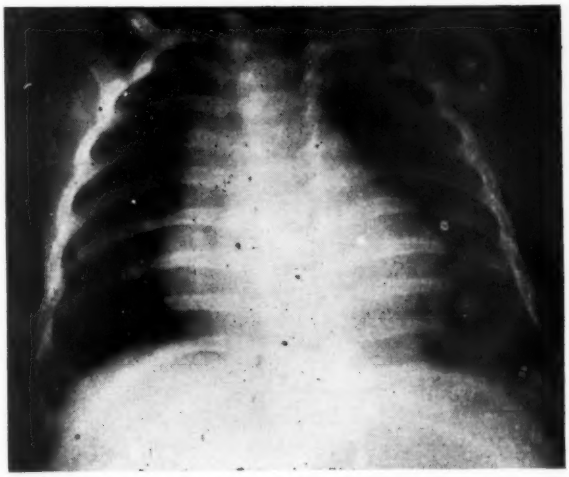

FIG. 1.—Radiograph of chest showing enlarged cardiac shadow with increase of right atrium and loss of muscle tone.

examination of the skull and long bones disclosed evidence typical of rickets.

The electrocardiogram revealed a left ventricular preponderance with shortening of the P-R interval, a prolonged Q-T interval and inversion of T in the praecordial leads (Fig. 2).

As far as the differential diagnosis was concerned, the dominating symptoms were those of acute cardiac insufficiency. Various possible diagnoses were entertained initially. For instance the cardiac type of infantile paralysis the more so as the patellar reflexes were abolished; fibroelastosis; after the onset of neurological signs, rhabdomyoblastosis, which, associated with tuberous sclerosis, gives the so-called Bourneville's disease; and lastly diphtheria, in spite of the lack of any suggestive history or findings.

The definitive recognition came *ex iuvantibus*. A dramatic change in the apparently hopeless condition

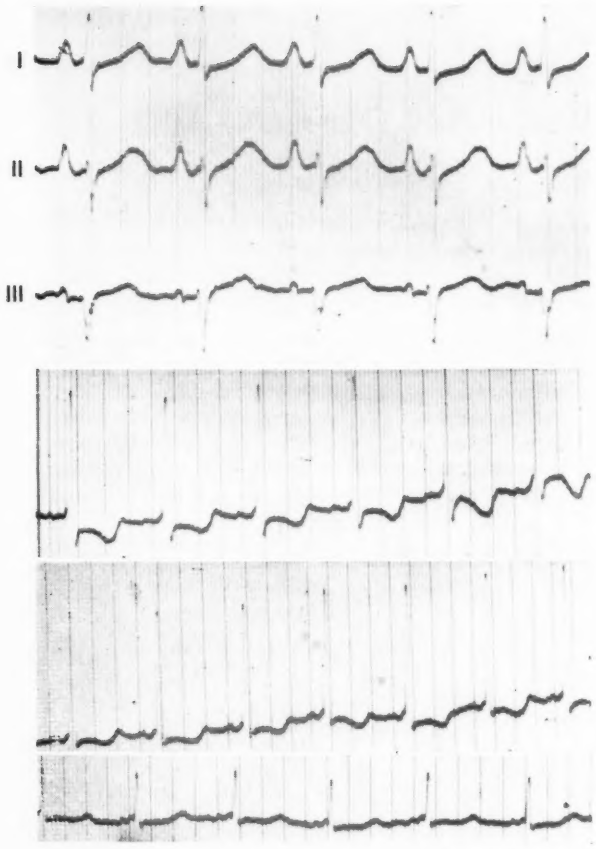

FIG. 2.—Electrocardiogram in case of frank beriberi in infant.

of the patient following the administration of vitamin B_1 on tne third day after admission anticipated the diagnosis.

Forty-eight hours after the intramuscular administration of thiamine, in a dose of 50 mg. daily, the appetite returned rapidly and also the normal skin colouration. The dyspnoea disappeared and respirations dropped to 40 to the minute, the pulse decreased to 120 per minute and there was a progressive decrease in all dimensions of the heart, the sounds of which became louder and clearer. The knee-jerks reappeared on the seventh day. In the second week the heart returned to its normal limits (Fig. 3) and phenylpyruvic acid could no longer be found in the urine. From this time on vitamin B_1 was continued orally. The boy was discharged 23 days after admittance.

Discussion

Special mention should be made of the excretion of phenylpyruvic acid in the urine of this patient. He was a full-term baby and did not receive a high protein diet. His mental development did not seem to be affected, his hair was rather dark, the sclerae white and there was no muscular hypertonicity,

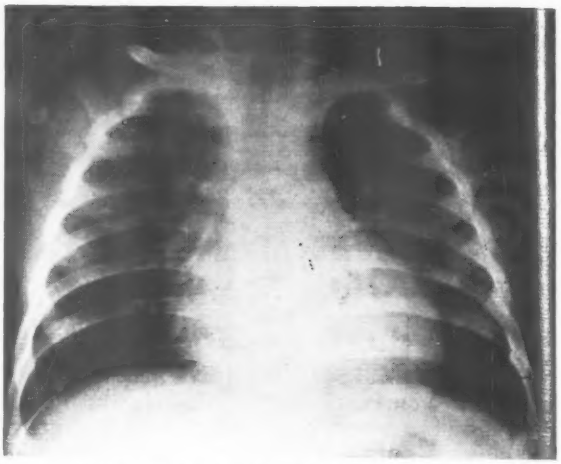

FIG. 3.—Radiograph showing heart within normal limits after two weeks' administration of vitamin B_1.

tremor or patchy eczema; he excreted a pale urine containing no reducing properties, and there was no dark staining on his diapers; there was no suggestion either from the history, physical examination or from radiographs of the long bones to suggest scurvy. We consider therefore that phenylpyruvic oligophrenia, tyrosyluria of premature infants, alcaptonuria and vitamin C deficiency, all four of them conditions sometimes associated with phenylpyruvic acid in the urine, were excluded.

As we could not relate phenylpyruvic acid excretion to any of these four disorders, we suppose, though possessing no certain proof, that pyruvic acid, present in excess in the tissues during vitamin B_1 deficiency may be conjugated with phenyl radical either in the liver or kidneys and then excreted in the urine. It is well known that phenols are detoxified in the liver by conjugation with sulphuric acid or organic acids. Moreover, Closs and Fölling (1936) have demonstrated the presence of phenylpyruvic acid in the urine of rats suffering from artificially produced hypothiaminosis.

Summary

A 4-month-old infant fed on a butter-flour mixture, prepared from overmilled wheat meal, developed frank beriberi with cardiac enlargement and circulatory failure, a grunting cry and loss of the patellar reflexes. All these symptoms disappeared after giving him large doses of vitamin B_1.

This appears to be the first case of true infantile beriberi reported in Europe.

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WILLIAM HEBERDEN'S CASES OF ANAPHYLACTOID PURPURA

BY

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From Addenbrooke's Hospital, Cambridge

(RECEIVED FOR PUBLICATION SEPTEMBER 9, 1957)

Of William Heberden (1710-1801) Dr. Wells, in a letter to Lord Kenyon, wrote, 'Dr. Heberden, my Lord, stands in a manner alone in his profession. No other person, I believe, either in this or any other country, has ever exercised the art of medicine with the same dignity or has contributed so much to raise it in the estimation of mankind'. Heberden's modesty, integrity and scholarship earned him the admiration of his contemporaries and the affectionate respect of his biographers. In his writings he recorded accurate observations of disease in a simple lucid style. He contributed many papers to the Philosophical Transactions of the Royal Society and to the Medical Transactions of the College of Physicians. He is now remembered particularly for his descriptions of chicken pox, angina pectoris and the nodes in osteo-arthritis.

His 'Commentaries on the History and Cure of Diseases' was published by his son William Heberden in 1802, the year after his death, first in Latin and later in English. The Commentaries were built up gradually from notes taken from day to day during his active professional life. They were revised each month and expanded or modified until 1782, after which year no significant alteration was made. Chapter 78 of the Commentaries, entitled 'Purpureae Maculae', includes two brief case reports.

> 'A boy, four years old, for several days had swellings rise on his knees, legs, thighs, buttocks, or scrotum. The part affected was not discoloured, and when at rest, was easy, but could not be moved without some degree of pain. Together with these swellings there appeared red spots sometimes round, sometimes angular, a quarter or half an inch broad, which on the second day became purple, and afterwards yellow, just as it happens from a bruise. The child continued perfectly well in all other respects. These swellings ceased to appear in about ten days; but the red spots continued coming out a few days longer.
>
> 'Another boy, five years old, was seized with pains and swellings in various parts, and the penis in particular was so distended, though not discoloured, that he could hardly make water. He had sometimes pains in his belly with vomiting, and at that time some streaks of blood were perceived in his stools, and the urine was tinged with blood. When the pain attacked his leg, he was unable to walk; and presently the skin of his leg was all over full of bloody points. After a truce of three or four days the swellings returned, and the bloody dots, as before. These dots became paler on the second day, and almost vanished on the third. The child struggled with this uncommon disorder for a considerable time, before he was entirely freed from it.
>
> The first of these boys immediately grew better after being gently purged: the other took a decoction of the bark for several days without any manifest good effect.'

These children were certainly suffering from anaphylactoid purpura. Gairdner (1948) gives Willan (1808) the credit for the first description of a patient with this syndrome. Neither Heberden nor Willan differentiated the syndrome from other forms of purpura but Heberden clearly described the association of the skin lesions with gastro-intestinal symptoms, joint pain and haematuria. Although Schönlein (1837) and his pupil Henoch (1874) are rightly commemorated for establishing the syndrome as a distinct entity, Heberden's admirable clinical description does not deserve the neglect which has been its fate.

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BOOK REVIEWS

The Year Book of Pediatrics. Edited by SYDNEY S. GELLIS. (Pp. 469. $7.50.) Year Book Publishers, Chicago. 1957-58.

The Year Book of Pediatrics for 1957-58 is in the tradition and up to the standard of its very competent predecessors. The notice taken of non-American activities has been rising over the years and in the present volume more than one third of the articles abstracted are not American; thus a much broader picture of the year's work in children's medicine is presented. In a mixed bag such as this, providing something for everyone, the quality of the work abstracted will inevitably be variable, yet for anyone wishing to see what has gone on in paediatrics in the past year this book will be more valuable than any other; and if the invited comments by selected experts which follow some of the abstracts are as irritating as ever, they are in the tradition of this Year Book and one must presume that there is a demand for them in some quarters or they would not be there.

Paediatrics. Supplement 1957. Edited by WILFRID GAISFORD and REGINALD LIGHTWOOD. (Pp. v+157; 45 figures. 35s.) London: Butterworth. 1957.

This is the second supplement of Paediatrics for the Practitioner. It contains original contributions by various specialists, on gamma-globulin and immunity, prophylactic immunization, steroid therapy, skin tuberculosis, congenital heart disease, funnel chest, cysts of the neck, the testes and penis, and galactosaemia. In addition there is a further Noter-up or Bringer-up-to-dater which entirely replaces the previous edition.

The volume is as factual and practical as those preceding it and the presentation maintains the high standard set. It makes one miserable to note that the combined price for the set of volumes is now £14 10s. 0d.

Pediatric Profiles. Edited by BORDEN S. VEEDER. (Pp. 267.) St. Louis : C. V. Mosby. 1957.

As the illustrious men of their day die they leave behind them many forms of memorial. Not least of these perhaps is the enduring memory which lingers in the hearts and minds of those who knew them. A later generation may read their writings and they may also be known by one or other alteration they have made to the subject or discipline they adorned. But scientific writing tends not to evoke the personality of the writer, nor does a ward block named after someone conjure up to a younger generation a picture of the man whose memory it honours. In order that succeeding generations should know something not only of the scientific contributions of the great but also something of their personalities the *Journal of Pediatrics* in 1953 started to acquire and publish a series of word pictures of great paediatricians, written by people who had known them intimately. Thirty of these have now been collected in this volume entitled *Pediatric Profiles*, in which worldly achievements are incidental and subordinate to the character and personality of the subject.

The original idea was that only Americans should be included and that they should be not still living, but as the Editorial Board of the *Journal of Pediatrics* progressed, however, they realized that some men who had exerted a national influence on American paediatrics were not in fact Americans, and the scope of the subject matter had to be widened to include some British and Continental paediatricians; we thus find Jacobi, the first President of the American Pediatric Society, next to Sir Thomas Barlow, while Abt is followed by Jundell of Sweden, Still, Poynton, Cooley and Brennemann. What a series of subjects for their authors !

Pediatric Profiles will find a welcome wherever the discipline of paediatrics is followed. To the existing generation, many of whom will remember some of the characters depicted in the book, memories will be re-awakened vividly, while coming generations of paediatricians will find first-hand appraisals of the personalities of men whose work will be bound to influence their daily lives and doings. The book ends with two nostalgic little pieces of what has been called anecdotage, one on paediatrics in Vienna at the turn of the century by Bela Schick and the other by the editor, Veeder, an account of his first National Pediatric Meeting in Washington in 1910.

Orthopedic Surgery in Infancy and Childhood. By Albert Barnett Ferguson, Jr. and five other contributors. (Pp. xii+508; 504 figures. 120s.) London: Baillière, Tindall and Cox; U.S.A.: Williams and Wilkins. 1957.

This book aims to fulfil the need for a comprehensive text-book of the surgery of the locomotor system (excluding fractures) as applied to children.

The authors are to be congratulated on the success of their venture and particularly on their presentation of those aspects of the subject which are controversial. In general their practice is in accord with that of orthopaedic surgeons in this country and such differences as exist are in emphasis rather than of a fundamental nature.

The readers of this journal will find much to interest them in this book which concentrates more on principles of management than on details of surgical treatment. Most of the common orthopaedic conditions are well described and rarities mentioned in sufficient detail to satisfy the needs of those not primarily concerned with this speciality.

Physicians will probably appreciate the concise and clear account of disorders of calcium and phosphorous

metabolism contributed by Klein. The section on generalized disorders of the skeleton by Ferguson, although using some terms unfamiliar to British readers is stimulating and pursues an aetiological theme convincingly and with conviction. There is a balanced review of indications for treatment in cerebral palsy and when surgical measures are mentioned emphasis is on the few well-tried and successful procedures such as triple arthrodesis, and even these are discussed in a cautious way. The many operations described which have a theoretical rather than a practical application are rightly left out.

The illustrations are excellent and help both to clarify and amplify the text. The bibliography is well chosen and affords a good introduction to further reading in those subjects which in a book of this nature must be covered briefly. This book should be in the library of every orthopaedic and paediatric hospital and department, but its price, £6, will probably exclude it from the personal collection of many paediatricians and surgeons. This is a pity.

Chirurgie Préventive de la Tuberculose Ostéo-articulaire. By R. KAUFMANN. (Pp. 174; 49 figures. Fr. fr. 2,000.) Paris: Doin. 1958.

The author begins 'when this work appears, M. Blondin will have proved before the Academy of Surgery that we know how to cure and above all prevent caries of the vertebrae. Osteolysis which precedes caries is a non-specific reversible state following infection of the adjacent soft parts. Once they have been drained the bone becomes normal'. The primary lesion is lymphatic and the author advises excision of the diseased lymphatic glands and abscess leaving the wound open. Despite endless repetition and the obvious sincerity of the author the reviewer remains unconvinced. It would have been better to include more evidence instead of referring the reader to seven previous publications. Despite these criticisms it is a refreshing book which stimulates thought on a subject which seemed to be cut and dried.

Cryptorchism. By CHARLES W. CHARNY and WILLIAM WOLGIN. (Pp. viii+140; 28 figures. 45s.) London: Cassell. 1957.

This book covers the whole field of cryptorchidism except for intentionally making only brief reference to its endocrine aspects.

The various causes of non-descent are considered. The gubernaculum appears to play little or no part. The importance of short testicular blood vessels is stressed. Failure of development of the processus vaginalis and its descent into the scrotum is usually accompanied by descent of the testicle. Excluding gross endocrine disorders there are two main causes of non-descent of the testicle: mechanical difficulties or an inherent incapacity of the testicle to respond to normal gonadotrophic stimuli.

The chapter devoted to pathological findings forms the kernel of the book. These findings have been obtained by testicular biopsies done at operation and to check treatment by operation and by chorionic hormone. The opinion is given that the follow-up of a series of cases is almost valueless without serial biopsies, although, of course, it is realized that seminal analyses afford assessment in cases of bilateral cryptorchidism. It appears that little histological difference exists before the age of 9 or 10 years between the scrotal and non-scrotal testis. The degree of pathological change depends more on the age of the patient than the degree of descent. With the histological material available it was not possible to determine the relative importance of congenital testicular deficiency and the effect of unfavourable environment on the testicle. The histology investigations confirm the previously established findings that in the adult unilateral cryptorchidism allows normal libido, potentia and fertility whilst in bilateral cases it is often only the fertility that is absent.

The second part of the book deals with symptomatology, complications, diagnosis and therapy. The authors' study of the literature and their own experience confirm that many complications are commoner in the undescended testicle than in the normal. Of especial importance are trauma, torsion, associated hernia and malignancy—besides, of course, infertility. It appears that the undescended testicle is about 33 times more liable to become malignant than is the scrotal. It also appears that the intra-abdominal testicle is four times more liable to malignancy than is the inguinal type. The malignancy is usually a seminoma. The point is made that when this occurs in a testicle that has been brought down by orchidopexy, the inguinal lymph nodes should be excised as well as the testicle and its coverings. The authors found very little evidence that psychic disturbances occurred frequently or played an important part.

Possible treatment by gonad-stimulating hormone (chorionic gonadotrophin) followed by androgen is discussed. Great importance is given to the avoidance of overdosage because of the likelihood of harming the other (scrotal) testis. The authors could not be counted as strong supporters of this sort of therapy; they do point out, though, that such treatment differentiates testicles that will and will not descend without operation. The authors attach no value to this therapy as a pre-operative measure to facilitate the operative technique.

They refer briefly to the various techniques of orchidopexy and stress the importance of adequate mobilization of both the testicular vessels and the vas deferens.

Basing their opinion on the histopathology of biopsy specimens which indicates the changes of physiological puberty as beginning at about 9 or 10 years of age, the authors feel that all treatment by hormones or by operation can safely be left until that age. As stated above they accept the use of hormones as a diagnostic and a therapeutic guide but no more. Regarding orchidopexy, in unilateral cases it is felt that the value of this operation is open to question. In these patients fertility is already assured by the other scrotal testis and investigations have shown very poor results of spermatogenesis following orchidopexy. Furthermore, in some cases total atrophy has followed operation. Thus in prepubertal patients orchidopexy is not recommended.

The patient should be watched. Certainly in adults there can be no reason for doing an orchidopexy. In bilateral cases orchidopexy before the age of 10 years is advised as it is the only hope of preventing certain sterility.

If in the repair of a hernia satisfactory orchidopexy is impossible or if the testis is found to be unusually small, then it should be removed provided the other testis is normal.

The results of treatment by gonadotrophins and by operation are reviewed as is the literature. It is pointed out that descent of the testicle into the scrotum is of itself not evidence of successful therapy. It is spermogenesis that is so important to aim for.

The material is well presented. The microphotographs are good and the references and bibliography excellent. These features make for pleasant reading of matters that require to be much more widely known.

The Lower Urinary Tract in Childhood. By S. R. KJELLBERG, N. O. ERICSSON and ULF RUDHE. (Pp. ix.+298; 265 figures. 126s.; 18.00$.) Chicago: Year Book Publishers; London: Interscience Publishers. 1958.

This is primarily a radiological monograph and fully upholds the very high standard which we have come to expect from Swedish publications in this field. The illustrations are so numerous and well-reproduced that this volume will undoubtedly become an indispensable work of reference for x-ray departments undertaking urological investigations in children. Good chapters on anatomy and physiology preface the discussion of pathological conditions, but in the latter the text is so sparsely scattered amongst the illustrations that the thread of the argument is sometimes hard to follow. It is interesting to note that, as in other centres where radiography is given precedence over endoscopy, these authors lay great emphasis upon the role of urethral valves as a cause of urinary obstruction and enuresis, while 'bladder neck obstruction' is regarded as rare. The chapter on ectopic ureterocoele is particularly valuable, as might be expected from Dr. Ericsson's previous studies.

Clinical Application of Hormone Assay. By JOHN A. LORAINE. (Pp. xii+368; 305 figures. 30s.) Edinburgh and London: E. & S. Livingstone. 1958.

Since the war hormone assays have passed increasingly into the province of the clinician and the clinical research worker; they are no longer confined to the physiologist concerned with pure research, or the pharmacologist attached to a drug house. Clinical problems have brought their own peculiar difficulties to assay work, the chief of which are the minute quantities of the hormones present, as a rule, in biological fluids, and the extreme complexity, i.e., impurity, of the fluid which has to be tested. That these problems have been posed but by no means solved is illustrated by the fact that in five of the nine chapters which deal with bio-assays in this book, the author concludes with the statement that the available techniques are inadequate for routine application in the clinical field and that further work is necessary in methods of extraction of the hormones from blood and urine.

A chapter is devoted to every hormone, except the thyroid, the parathyroid and the gastro-intestinal hormones, and each contains a brief description and evaluation of the possible methods of assay, with a summary of the principal findings in normal and in pathological conditions. The physician who is interested in endocrinology will find the book easy to read and entirely lacking in complicated diagrammatic speculations which often confuse rather than clarify. The specialist will find in it an excellent and critical introduction to work in each field, with frequent suggestions as to what needs to be done.

It is a commonplace that biochemical methods should, if possible, replace biological methods, and this is particularly true in the clinical application of hormone assay. Clearly biological work can hold its own where fundamentally new discoveries are concerned, but the doctor is concerned with an individual patient and the superiority of chemical methods in this report is unquestionable. This is brought out very well by Dr. Loraine in his chapter on the oestrogens. The concepts which emerged from the earlier biological work have not, in the main, been challenged by the subsequent chemical studies, but what the latter have produced are firm figures by which the normal can be distinguished from the abnormal.

Infant Feeding and Feeding Difficulties, 3rd ed. By PHILIP EVANS and RONALD MAC KEITH. (Pp. viii+293; 66 figures. 16s.) London: J. & A. Churchill. 1958.

For the third edition of this now well-established handbook on infant feeding Dr. Mac Keith alone is responsible. There is evidence of revision in all parts of it and perhaps most noticeably in the chapters on practical manoeuvres and the physiological aspects of lactation. The section on diets has been extended to include modern work on inborn errors of metabolism.

That a third edition has been called for seven years after the book originally appeared is at once an indication of the advances which have been made in infant feeding in this period and of the popularity of the book.

Les Regimes du Nourrisson Bien portant ou Malade. By P. DELTHIL. (Pp. 346. Fr. fr. 3,350.) Paris: G. Doin. 1957.

The publishers comment that there are few practical books on infant feeding, that the best of them date from more than 30 years ago and do not represent present ideas and that the comprehensive treatises do not give clear enough guidance. Dr. Delthil's book is 330 pages long, well-printed and clearly set out and may well be a considerable advance on what has been available in French up till now. However, as far as the present ideas on infant feeding in Scandinavia, North America and Great Britain are concerned, it is far from up to date. This might represent a justifiable French decision not to

follow fashions popular in other countries but that is not a complete answer. The attitude represented here is not only old-fashioned but is also inefficient, just as ours was 30 years ago. For example, insufficiency of breast milk is said to be revealed by falling-off of the weight curve, pallor and lack of tissue firmness of the child, sometimes by digestive troubles, false diarrhoea or vomiting. Do not French babies announce their hunger by crying? Test weighing is recommended, it being said that in the second month it should be '110 grms to 120 grms' and in the third month '125 grms to 135 grms'. Do not French babies vary widely in their individual needs? The section on breast feeding is too brief and, although it includes a table of amino-acids contained in breast milk, it does not refer to the draught reflex, knowing about which is an 'éclatante' aid in helping mothers to breast feed successfully. There is nothing about the prevention of cracked nipples and, in saying it is sometimes necessary to suspend suckling, no mention is made of the need to express the milk to avoid engorgement when suckling is omitted. A proper knowledge of the physiology and detailed management and difficulties of breast feeding would be a better way of increasing the number of women successfully breast-feeding than the remedy the author recommends, which is, 'Convinced of the striking superiority of breast milk, doctors should proclaim it incessantly and devote themselves to a continued propaganda'. One could make minor criticisms; for example, under renal acidosis, anorexia is mentioned as an important symptom but renal acidosis is not given when the causes of anorexia are discussed.

Dr. Delthil was formerly Chéf de Laboratoire at the Hôpital des Enfants Malades. Whether he is now in practice I do not know. However, there are doctors in Paris who know what immense practical help knowledge of the physiology of lactation and child-centred management, instead of mechanical management of the individual child's feeding, can give. I am inclined to suggest that one of the small English text books on infant feeding adapted by a French paediatrician might be found of greater practical value than this particular work. I am sorry to say this for there is much that is very good and very acceptable in the book but the author seems to me to have missed the chance of including the last 20 years' advances in the practice of successful infant feeding.

Treatment of the Child in Emotional Conflict. By HYMAN S. LIPPMAN. (Pp. x+298. 45s.) London: McGraw Hill. 1956.

Some such book as this should be read by every paediatrician in training. Child guidance is an established adjunct to child health, and the report of the Commission of Child Guidance in this country visualizes considerable extension of this policy. Although the general pattern of all child guidance is similar, the underlying psychiatric and psychological principles in each particular clinic are to a large extent dependent on the training and principles of the consulting psychiatrist in charge. This book is a concise, straightforward exposition of the full Freudian outlook on child guidance. It is written in plain English for the intelligent, but not specially trained, medical personnel, and it is only necessary to become fully acquainted with the precise meaning of such terms as 'ego', 'super-ego', 'id', and a few others, to be clear of the meaning of every page. Since its psychological orientation is totally Freudian, as developed for child guidance by Melanie Klein, Susan Isaacs, Aichorn and others of a rather closely knit group of workers, it will certainly not meet with universal acceptance by paediatricians or child guidance workers in this country. Nevertheless, every page is written with such seriousness and such intensity of understanding and sympathy for the sufferings of the emotionally disturbed child, and so much of it has universal application, that it might well be read with equally responsive understanding by all those engaged in child health work.

The book is divided into seven sections: the first, of four chapters, discusses the general symptoms of emotional complications in childhood and the kind of influences it may exert on mental growth and development. It also takes the reader through the general arrangements and methods of therapy, the working and the staffing, of a particular child guidance clinic in the United States. The following four sections deal successively with four major clinical groupings of emotionally disturbed children, namely, the 'Neurotic Child', the 'Child with Personality Problems', the 'Child who "Acts Out"', and lastly the 'Child with a Tenuous Hold on Life'. Each of these major divisions of from three to six chapters, takes the reader through particular individual types of maladjustment illustrated by brief appropriate extracts from case notes. The last section discusses in general terms the prevention of social and emotional maladjustment and defines some of the wider aims of child guidance.

The author is obviously convinced that with adequate psychotherapy, that is with therapy often lasting over two or three years, but sometimes very much less, children who would otherwise grow up with such maladjustment as to make their adult life burdensome to themselves and others, can eventually be salvaged sufficiently to grow up reasonably well-adjusted human beings. This is a considerable claim, particularly when one reads some of his fearful case notes. But what he does not make quite so clear is how successful a widely distributed network of child guidance clinics will prove to be in dealing with the day-to-day maladjustment of quite a large proportion of the child population. If adult maladjustment has its roots in childhood, which is widely accepted, this latter problem is of vast importance and would be the decisive justification for the large and expensive set up that exists in America and to a lesser extent in this country.

Deafness, Mutism and Mental Deficiency in Children. By LOUIS MINSKI. (Pp. viii+82; 14 figures. 12s. 6d.) London: William Heinemann. 1957.

The main theme of this book is the importance of distinguishing between deafness, mental deficiency and emotional disturbance in children with severe delay in speech development. A brief account is given of two residential units set up by the author to investigate and

treat such cases and there are additional sections on deafness in children and psychological testing.

For such a short book there is too much inessential material. For example, almost one-third of the book is devoted to psychological testing, while most of the results of the author's important original work are compressed into some 15 pages. Would not a paper confined to the original work and published in a weekly journal have served the author's purpose better?

It is unfortunate that the earlier Australian figures on the risk of congenital defects following rubella in pregnancy should be quoted, now that prospective investigations have shown them to be fallacious.

These are, nevertheless, minor criticisms and should not be allowed to hinder the promotion of such a worthy cause.

L'Enfant Inadapté. Rôle Médico-social du Médecin. By L. Michaud and D. J. Duché. (Pp. 316. Fr. fr. 3,600.) Paris: G. Doin. 1957.

In this book the possible origins of maladjustment are considered in a most comprehensive manner. The authors' concept of maladjustment differs from ours, for they use it to mean the child who is at a social disadvantage from both physical and mental handicap. The physical causes are dealt with in great detail and hardly a condition has been omitted, but little emphasis is placed on the relative frequency or importance of different diseases, the rare and the commonplace being given equal attention. As to the developmental-psycho-educational aspects these are dealt with in their own particular fashion. There is no 'school' view-point advocated and their eclecticism is all embracing from Melanie Klein to leucotomy. The value of a work of this kind is limited, particularly when our knowledge of where and how things go wrong socially and physically in children's lives is so abundant. As a general review it has a place for those beginning to study children but its unevenness detracts from its otherwise potential value.

Cleft Palate and Speech, 4th ed. By MURIEL E. MORLEY. (Pp. xx+271; 86 figures. £1 7s. 6d.) Edinburgh and London: E. and S. Livingstone. 1958.

That this book has appeared in four editions since it was first published 13 years ago speaks well for its all-round excellence. The title *Cleft Palate and Speech* is a well chosen one because it indicates the theme which runs throughout the book, that treatment must be directed primarily towards achieving the happy result of perfect speech, and that such an object can only be attained by close cooperation between various experts, including surgeon, orthodontist and speech therapist. The book is particularly valuable in this respect and enables each to understand the work of the others, thus coordinating their efforts towards the common goal.

The subject matter is extremely comprehensive and is presented clearly and scientifically. The opening chapters encompass the embryology, anatomy and inheritance of cleft palates. The difficult and controversial subject of the mechanism of palatopharyngeal closure is very reasonably presented, and is followed by the management and surgical treatment. The chapter on the development of surgery will help many readers to orientate themselves in the history of the various procedures and to understand current trends. To most speech therapists who have not been able to watch and study surgical methods themselves this account will be of considerable help. Speech and speech therapy are discussed in the latter half of this book.

There is much that is new in this edition and it is obvious that the author has kept abreast of the surgical development in this field. This book must be essential to all speech therapists and is one which could be read with profit by all concerned with the treatment of cleft palates.

Fluoridation of Public Water Supplies. Report of the Commission of Inquiry, 1957 (appointed by the Governor General of New Zealand). (Pp. 240. 8s.) Wellington: Departmental Fluoridation Committee, Department of Health. 1957.

This report shows clearly that the fluoride content of water in New Zealand should be increased. The amount of dental caries is at present devastating and could be halved. The Commission has found that no harm need be anticipated from this measure. The spectre of chronic fluoride poisoning has been laid with reasonable certainty. Justice has been done to the scientific evidence; moreover, by public hearings it has been seen to be done to the Papatoetoe Anti-fluoridation Society, the New Zealand Organic Compost Society and other representatives of man's right to water, however natural.

While few Cockneys would care to exert their right to imbibe Father Thames in his natural state, this report serves to remind us that the fluoride content of much British water is still inadequate.

PRINTED IN GREAT BRITAIN BY HEADLEY BROTHERS LTD 109 KINGSWAY LONDON WC2 AND ASHFORD KENT